RARE DISEASES AND SOME DEBATABLE SUBJECTS

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SECOND EDITION REVISED WITH ADDITIONS

For the classification and understanding of Rare Diseases and Syndromes the study of developmental dysplasias hamartomata and nævi (in the broadest sense of the word nævus) as well as genetic factors —especially inborn metabolic and other functional errors and tendencies—should play a most important part



S T A P L E S   P R E S S

STAPLES PRESS LIMITED   STAPLES PRESS INCORPORATED

M ide lle Plac   L d n   70 E st 45th St t   Neu York

CONTENTS

FIRST PUBLISHED 1946
SECOND EDITION REVISED WITH ADDITIONS 1947
REPRINTED 1948

SET IN 11 ON 12 MONOTYPE BASKERVILLE



Made and printed in England by
STAPLES PRESS LIMITED
at their Great Titchfield Street London establishment

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FOREWORD

During the last thirty years it has repeatedly been suggested to me to write a book on Rare Diseases In the present little volume I have not included anything about leukæmias polycythæmias anæmias Hodgkin s disease and other reticuloses myelomatosis, atypical (primary) amyloidosis, familial hæmolytic jaundice infantile acrodynia myositis ossificans glycogen accumulation disease (v Gierke), certain types of cholesterol deposition aortic co arctation and developmental abnormalities of the blood vessels certain developmental abnormalities of the skeleton and other diseases and developmental abnormalities which formerly from time to time have specially interested me I have, however here considered a great number of dysplastic and other diseases and syndromes (*see* Index at end) I hope the reader will excuse occasional repetition

I wish to thank the publishers and editors of the medical journals mentioned in the various sections—especially the *British Medical Journal* the *Lancet* the *Proceedings of the Royal Society of Medicine* the *Annals of the Rheumatic Diseases* the *British Journal of Dermatology and Syphilis* the *British Journal of Children s Diseases* and (many articles) the *Medical Press and Circular*—for kind permission to reprint or otherwise to make use of my published articles

F P W

January 1946

BY THE SAME AUTHOR

ASPECTS OF DEATH AND CORRELATED ASPECTS OF LIFE IN ART EPIGRAM AND POETRY C ntribut ons towa ds an Anth logy and an Icon g aphy of the Subj ct Illu t ted p cially by M d ls Engr ed Gem Jewel I Ant que Pott ry Etc Fou th Ed ti n Lond T F h r Unwin 19 *(O t of p nt)*

MEDALS AND MEDALLIONS OF THE NINETEENTH CENTURY RELATING TO ENGLAND BY FOREIGN ARTISTS Lon l Bernar l Q rit h 1894 *(O t of print)*

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LIPODYSTROPHIA PROGRESSIVA Lo don Adl rd & S n 1918

TRAUMATIC PNEUMONIA AND TRAUMATIC TUBERCULOSI L ndon A ll r l & Son 1916

THE RELATIONS OF TUBERCULOSIS TO GENERAL BODILY CONDITIONS AND TO OTHER DISEASES (Th F t M t h ll Le t h f e th Royal C ll g of Phy Lon lon) W th n App n l o Lit tur r l t g t th ubj t f So lle l Sy ntan o ld p th In um th ax L lon H K Lewi & Co Lt l 19 I *(Out f p int)*

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(W th S H a n W b) THE MINERAL WATERS AND HEALTH *RESORTS OF EUROPE L n l n S n th El l & C F t Ed t n 1896* S ond Ed t n 1898 *(Out f)*

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LETTERS ON CONTEMPORARY SUBJECTS I t ly p nt d 1943

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MORE *THOUGHTS* AND COMMENTS OF A DOCTOR II VIII S t Ii n L nd H K Lew & C Ltd 1946

I

ON RARE DISEASES AND SYNDROMES, WITH SOME EXAMPLES[1]

I SHALL first quote from an old paper of mine on the subject [2]

A disease, as the term was formerly used was a group of various signs and symptoms It was, in fact, what we now call a syndrome or symptom complex When the cause or causes of such a syndrome have been more or less discovered the syndrome becomes a disease, but many syndromes of unknown causation are still called diseases, and disease in such cases is only a courtesy title In Paget s bone disease, which we call osteitis deformans, though an age factor and occasional familial incidence are admitted, we still do not know the main cause or causes and the relation of the condition to processes of osteoporosis Perhaps an osteosclerotic reaction towards some unknown osteoporotic agent plays an important part in producing the clinical and pathological features of osteitis deformans (ordinary as well as unusual forms)

Out of many cases of fibrocystic disease of bones (using the term in the sense of a syndrome) a definite real disease has been separated due to hyperparathyroidism from the presence of a functionally active endocrine tumour a parathyroid adenoma the surgical removal of which may lead to cure Before the discovery of the plasmodium of malaria ague was strictly speaking, only a syndrome which clinically at one time included various cases of cholangitis malignant endocarditis etc as well as true malaria Though it is probably correct to speak of Cushing s pituitary disease it is hardly correct to speak of Cushing s syndrome since the actual clinical syndrome in question is not peculiar to pituitary basophilia (basophilic adenoma) and was recognized before Cushing s important work on the subject

Having to some extent explained my use of the terms syndromes and diseases I come to the question of the value of clinical societies in their recognition study and treatment I believe that further progress in medical knowledge will largely be due to the study of rare diseases and syndromes For one common disease or syndrome there are several rare ones the study of any of which can help scientific progress as much as the study of a common one Though I admit that special knowledge of common diseases is required for

[1] *Medical Press and Circular* 1936 215 87
[2] *Brit Med Journal* 1937 2 930 (with slight alteration)

the alleviation of the vast majority of patients, the diagnosis even of common diseases can often not be established without a knowledge of rare ones, which have to be excluded in coming to the correct diagnosis Rare diseases are like the proverbial exceptions in so far as they prove (probant) or test the current rules and theories that have been set up about all kinds of diseases and morbid processes Pasteur said that more can be learned from investigating rare, apparently exceptional, cases than from ordinary typical ones That is to say, such rare cases are not really exceptions to Nature's laws, and by investigating them something more about Nature's laws can be ascertained

As I have above remarked the diagnosis of common diseases and syndromes is greatly facilitated by a knowledge of the rare diseases and syndromes which have to be excluded Such a knowledge is made relatively easy by the formation of clinical societies, it is impossible for anyone to become acquainted with many rare diseases and syndromes by means only of his own private or even hospital practice From a former member I heard long ago of the advantages obtained by having been a member of the Society of Clinical Observation in London, a predecessor of the Clinical Society of London, to which I myself belonged before it became the present Clinical Section of the Royal Society of Medicine

One of the many advantages of demonstrating puzzling or rare cases at such a society the transactions of which are printed has been so it seems to me, insufficiently acknowledged In a free country like England patients are fortunately—at all events in London—not compelled to keep to one doctor or one hospital, otherwise a patient with a rare disease or syndrome might be chained to the doctor who happened first of all to diagnose his condition until either cure was effected or the patient or the doctor died When such a patient decides to try a new hospital the inevitable inquiry which the new hospital makes is addressed to the medical or surgical registrar of the old hospital Much trouble is then saved if a reprint or printed excerpt of the account of the case from the proceedings of some clinical society can be sent in answer I wonder whether hospital authorities even now quite realize the advantages to be gained by supporting (or even founding) such clinical societies both in regard to the treatment of patients in their hospitals and in regard to the advancement of medical knowledge in general State clinical societies should claim a place in any Utopia of the future

In regard to clinical meetings I suggest it would be best to have the examination of the patients on a day preceding the discussion as this would enable members to look up their notes bearing on the cases and make the discussions more complete and profitable In this way real advance in knowledge is also more likely to be made

THE STURGE-KALISCHER DISEASE

AMONG the many rare congenital and developmental diseases of the nervous system—inborn diseases or abnormalities of development, potentially present at birth though often not or only imperfectly developed till some period of post natal life—is a curious dysplastic hæmangiectatic condition with which my name has



The Sturge Kalischer disease appearance of the patient

sometimes been associated especially in Sweden and America, involving parts both of the skin of the face and the meninges I happened to be the first (1922) to publish the radiographic appearances of the brain in a typical case of this kind and the condition

may be compared to such congenital and developmental dysplastic diseases, as Lindau's disease von Recklinghausen's neurofibromatosis, syringomyelia (and syringobulbia), and Bourneville's disease or epiloia (a syndrome including tuberous sclerosis of the brain and Pringle's nævoid telangiectatic type of sebaceous adenoma)

The patient was indeed a remarkable sight She was a rather obese young woman with a fleshy face, much of which, especially



The Sturge Kalischer disease Skiagram showing calcified meningeal hæmangiectatic lesion of the left cerebral hemisphere

the left side, was scarlet or purple owing to a very large telangiectatic nævus, on the left side she had an ox eye (buphthalmos congenital glaucoma) and the right half of her body was smaller than the left half and also hemiparetic pointing to a lesion on the left side of the brain [3] Because the X ray findings by Dr James Metcalfe in my case proved the existence of a more or less calcified

[3] Weber F Parkes *Journ Neurol and Psychopathol* 1922 3 134 and *Proc Roy Soc Med* 1928-9 22 431

and apparently festooned lesion on the surface of the left cerebral hemisphere, K H Krabbe[4] suggested the term Parkes Weber Dimitri disease V Dimitri,[5] in the Argentine having described the X ray findings in a similar case in 1923

But in 1935 Professor Hilding Bergstrand[6] called the condition the Sturge Weber disease because of the priority of Dr W Allen Sturge s account in 1879 I find that Dr Sturge[7] reported the case of a girl aged 6½ years with an extensive telangiectatic nævus, especially of the right side of the face and head right sided buphthalmos, and epileptic fits beginning in the left hand He concluded that the right side of the brain was also involved in the nævoid condition—and this in spite of adverse criticism by leading members of the London medical profession at the meeting as may be seen by the account of the discussion published in the *British Medical Journal* at the time R Schirmer of Greifswald[8] had already described the case of a man aged 36 with an extensive telangiectatic nævus especially of the left side of the face and left sided buphthalmos but he made no allusion to epileptic fits or brain disease

Much still remains to be discovered regarding the nature and pathogenesis of this disease but the priority of explaining the gross connexion of the various lesions in a typical case belongs to W Allen Sturge If anyone s name should be added to his it should be not mine or Dimitri s but Kalischer s, since S Kalischer in 1901[9] published an elaborate account of the post mortem findings in the brain of a child who was affected in the same way as Sturge s patient mine and those of others A study of the whole subject of telangiectatic and angioma like dysplasias and also the invariable absence of any hereditary or even familial incidence both tend to convince me that the Sturge Kalischer disease must be due not (like Recklinghausen s neurofibromatosis) to any genetic cause but to some accidental local injury (mechanical chemical or physical) to the ovum at some period after fertilization that is to say to the embryo during early intra uterine life

Krabbe K H *Arch Neurol and Psychiatry* 1934 **32** 737
Dimitri V *Rev Asoc Med Argent* 1923 **36** 63
Bergstrand H *Second International Neurological Congress* 1935 Abstracts p 124 Prof Bergstrand s colleague the brain surgeon H Olivekrona used the same term
[7]Sturge W A *Trans Clin Soc Lond* 1879 **12** 162
Schirmer R Von Graefe s *Archiv fur Ophthalmol* 1860 **7** Part I 119
Kalischer S *Arch f Psych u Nervenheilk* 1901 **34** 171 Dr K Blum has suggested the term Sturge Kalischer Weber disease

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[3]Weber F Parkes *Journ Neurol and Psych pathol* 1922 3 131 and *Proc Roy Soc Med* 1928-9 22 431

The cutaneous friability involves both the skin and its blood vessels Bruises occur much too readily A slight knock, especially where the skin lies directly over bone (e g over patellæ tibiæ olecranons), may produce a hæmatoma or actual splitting of the skin If there be an actual wound it tends to gape in spite of stitching and gives rise to a characteristic broad cigarette paper or papyraceous *atrophic scar* Such peculiar scars bruises and resulting pigmentation—especially the broad transverse atrophic scars over the knees—constitute the most obvious clinical manifestation of the Ehlers Danlos syndrome and Ronchese prefers to use the term dermatorrhexis (splitting or cleavage of skin) so as to stress this most important feature of the syndrome To my mind however, one should speak of the condition not as dermatorrhexis but rather as an abnormal tendency to dermatorrhexis—that is to say as abnormal friability or fragility of skin

Owing to the over extensibility of joints and the hereditary history in the pseudo hæmophilic condition described by G Sack (*Deut Arch Klin Med*, 1935 1936, **178** 663) in his article headed Status dysvascularis a case with peculiar friability of the blood vessels there can be little doubt that it should be regarded as a variety of the Ehlers Danlos syndrome

There is a superficial resemblance between some of the papyraceous scars in the Ehlers Danlos syndrome and so called idiopathic striæ atrophicæ of the skin—which develop idiopathically or after infectious diseases such as enteric fever in young persons especially about the period of puberty when general growth of the body is actively progressing—notably the transverse striæ patellares But the latter are never the result of actual wounds or traumata and never have the broad loose papyraceous appearance of the Ehlers Danlos scars and do not usually occur over the actual patellæ as those of the Ehlers Danlos syndrome do [3]

Bruises and slight hæmatomata in the Ehlers Danlos syndrome—lesions in the dermis or even involving subcutaneous tissue—should not be confused with the blood blisters (bullæ with more or less sanguineous contents separating the epidermis from the dermis) which are characteristic of dystrophic types of epidermolysis bullosa

[3]On the whole subject of idiopathic striæ atrophicæ of puberty *see* F P Weber *Lancet* 1935 2 885 and 1347 *Practitioner* 1917 99 453 *Brit Journ Derm* 1926 **38** 1 and remarks in discussion *Proc Roy Soc Med* Section Dermatol 19 4 **17** 45 and *Proc Roy Soc Med* Section Child 1927 **20** 11

THE EHLERS-DANLOS SYNDROME

I WILL now consider a developmental mesenchymal dysplastic syndrome, often of strikingly familial incidence [1] Strictly speaking it may claim to be a real *disease* like Recklinghausen's neurofibromatosis etc—of genetic mutational origin The complete form of the Ehlers Danlos syndrome is constituted by the association of three main gene abnormalities of development

(1) Over elasticity of skin, (2) over extensibility of joints and (3) *skin friability, of which the third is the most important constituent*

'Incomplete' cases with over elastic skin or over extensibility of joints or both, but without some degree of the characteristic



Atroph transverse scars ov r the patellæ in the Ehlers Danlos syndrome

cutaneous friability should hardly be included as examples of the Ehlers Danlos syndrome, especially when there is absence of typical more or le s complete cases in the family For instance a slight degree of over extensibility of fingers or thumbs i quite common amongst ordinary persons who are generally regarded as normal The over elasticity of the skin in the Ehlers Danlos syndrome may be limited to certain regions notably to the skin about the elbows and knees [2]

[1] *See* F P Weber *Brit Journ Derm* 1936 48 609
[2] On confusion in the terms chalasodermia cutis laxa loose skin dermatolysis elastic skin etc *see* F P Weber *Ur l and Cut Review* 1923 27 407

the same tendency to get bullæ on the feet in summer Rubbing is said to favour the development of the bullæ There have been many reports in America on this 'Cockayne or Weber Cockayne bullous eruption—*see* especially M Waisman Recurrent Bullous Eruption of the Feet and Hands (Weber Cockayne)—Localized Epidermolysis Bullosa *J Amer med Assoc* 1944 **124** 1247 containing many references to the recent literature *see also* J B S Haldane A New Pedigree of Recurrent Bullous Eruption of the Feet *Journ Heredit* (Baltimore) 1942, **33** 17 Dr E A Cockayne has suggested to me that there may be a Mendelian recessive as well as a dominant type This would account for the apparent absence of hereditary incidence in the case of the boy I saw first I do not know if there was any parental consanguinity, but there not rarely is in Jewish families like his Dr Cockayne points out that Kierland and Harrison s patient was the only member of his family known to be affected but he was a Jew, the son of cousins

SJOGREN'S SYNDROME[1]

HENRIK SJOGREN of Jonkoping (1933 and later), starting from the eye changes has succeeded in establishing the existence of a syndrome which in its complete form includes kerato conjunctivitis sicca xerostomia, rhinitis sicca pharyngitis sicca and laryngitis sicca but which is far more often incomplete There are chronic inflammatory changes in the parotid glands usually without suppuration but with recurrent exacerbations leading to permanent enlargement sclerosis or atrophy in irregular combination analogous changes in the other salivary and in the mucosal glands and also in the lacrimal glands (though usually without obvious clinical enlargement) The skin (especially the sweat glands) and stomach (acid producing glands) may be involved in some cases The clinical onset often more marked on one side than the other is intermittent and insidious and the patients are mostly middle aged women Clinical accompaniments may include acceleration of erythrocyte sedimentation alterations in the blood count body temperature and blood sugar curve arthritic symptoms and apparently sometimes the presence of focal infection

Sjogren concludes The morbid changes of the eye appear to find their simplest explanation in the fact that owing to extreme

[1] After *Brit Jour Ophthalmology* 194 **29** 299 and *Med. Press and Circ* 1945 **213** 253

In the Ehlers-Danlos scars there is sometimes a development of soft molluscoid or cyst-like pseudo-tumours of loose connective tissue, which, when present, have by some been regarded as constituting a *fourth clinical manifestation* of the Ehlers-Danlos syndrome. A *fifth clinical manifestation*, which may be admitted, is the occasional presence of peculiar freely movable nodules in the subcutaneous tissue of certain regions. These nodules, or 'spherules', are usually pea-sized or smaller and slip about under the skin, apparently in the superficial portion of the subcutaneous fat. By light pressure with the finger they can easily be moved an inch or considerably more without any pain or tenderness being complained of. In spite of their frequent hardness they have been found to consist of fat. I think, however, that they should not be termed 'lipomata'; they constitute evidence of a special kind of dysplasia in the more superficial portions of the panniculus adiposus. Apparently sprouting (bud-like) lobules of subcutaneous fat are formed, which by gradual thinning and atrophy of their pedicles become free or almost free bodies under the (unnaturally?) loose skin. Probably in time they may become minute oil-containing cyst-like spherules, with thickened or calcareous walls.[*]

FAMILIAL RECURRENT BULLOUS ERUPTION OF THE FEET AND HANDS IN HOT WEATHER

WHAT has been regarded by some as a local variety of epidermolysis bullosa is a disease more or less completely localized to the hands or feet or both hands and feet, characterized by a recurrent bullous eruption in summer, the exciting cause being the hot weather more than local traumatism. The familial incidence is very striking, as first pointed out by E. A. Cockayne (*Brit. J. Derm.*, 1938, **50**, 358), who, however, could find only one similar case recorded, namely, that in a boy aged 4 years by F. Parkes Weber (*Proc. Roy. Soc. Med.*, Section Dermat., 1926, **19**, 72). This boy is still troubled in exactly the same way in summer; the bullous eruption on his feet during summer makes standing painful and work in the Royal Air Force became practically impossible. In this particular case I could obtain no family history of any similar condition. I have recently been told of another case in a boy, aged 6 years, whose father has always had

[*] *See* 'Nature of the Subcutaneous Spherules in Some Cases of the Ehlers-Danlos Syndrome', by F. P. Weber and Janet K. Aitken, *Lancet*, 1938, **1**, 198.

glands of the gastro intestinal canal—suggest some derangement of the vegetative nervous system Some of the patients are of neuro pathic type

In a relatively early case that I have seen recently with Dr B Rogol the patient a woman (widow) aged 37 years, is recovering from her fourth attack In the intervals between the attacks she has hitherto appeared practically normal The attacks last about four weeks and are marked by dryness of her mouth with some swelling of the parotid and submaxillary salivary glands feeling of soreness and dryness of the eyes with some blurring of vision dryness of the skin, puffiness of the face and whole body notably about the ankles if not actually œdema Menstruation is absent or scanty during the attack There is some evidence of retention of fluid during the attack and increased urinary output during the period of recovery No fever has been detected Considerable muscular asthenia and general lassitude accompany the attack and may persist for some time after the attack Keratitis with reduced vision in one eye was reported in October, 1944 There has been over a year's interval between the present and the last attack The attacks have been in cold weather suggesting that winter favours some disturbance of the endocrinal balance Dr Rogol has noticed that a slight growth of hair on the lips (at least upper lip) and sides of the face coincides with the period of recovery (as marked by return of the salivary secretion), but gradually disappears spontaneously No drugs have hitherto been found to be of any real use in this patient

AN UNKNOWN DISEASE[1]

THE patient Mrs M W when aged 44 years was admitted to hospital on September 20 1937 with the history of having been ailing for the last four months with loss of body weight and pallor she also complained of pains in various parts of the body The ery throcyte sedimentation rate was extremely accelerated Skia graphic examination of the lungs (September 17 1937) just before the patient's admission showed much abnormal shadowing a rounded mass in the right upper zone and a mass also in the left upper zone She mentioned that not long before the commence ment of her illness she cut her left thumb whilst carving some cold lamb the wound took two weeks to heal In the hospital she fre quently had moderate fever (about 100 F) till about the middle

[1] After *Brit J urnal Dermat* 1939 51 13

diminution or complete abolition of the lacrimal secretion, the conjunctiva itself is obliged to provide for the entire secretion of fluid As the result of this a chronic œdema arises, which gradually leads to degeneration and atrophy of the epithelium One may suggest an analogous explanation for the secondary changes in the oral mucosa when they arise in cases of chronic xerostomia of any nature

In some cases the definite ocular changes are preceded by the salivary gland troubles, sometimes perhaps they may remain absent altogether

Non Ocular Features of Sjogren s Syndrome—Apart from the changes in the salivary glands and the mouth, non ocular features in cases that I have been able to see myself have included Dryness in the nose, pharynx and larynx, secondary dysphagia (Plummer Vinson syndrome), secondary cough (from dryness of mouth and pharynx), achlorhydria, dryness of skin dryness and atrophic change in vagina almost complete alopecia, accelerated erythrocyte sedimentation, hypochromic anæmia, low blood pressure low blood sugar, low blood calcium, Raynaud like blueness of hands and feet, telangiectasia on lips and tips of fingers, telangiectatic, pigmentary and scleroderma like changes in the legs (Sheldon s case 1938), delusional mental changes and occasional epileptic fits (Sheldon s case 1938)

It is possible that some of these features—e g the telangiectasia and the alopecia—may be superadded conditions not directly connected with the Sjogren s syndrome

In regard to the curious features in Sheldon s case I have heard of another case of Sjogren s syndrome with similar leg pigmentation

Ætiology—The primary cause of Sjogren s syndrome remains unknown though infective toxic allergic and endocrine factors as well as vitamin (especially vitamin A) deficiency have all been suggested It forms one of a group of syndromes or diseases specially affecting the female sex such as exophthalmic goitre lymphadenoid goitre, lipodystrophia progressiva superior idiopathic hypochromic and simple achlorhydric anæmias perhaps ulcerative colitis Simmond s pituitary cachexia and its so called functional counter part anorexia nervosa Though the ætiology has not been discovered, it appears to be of chronic inflammatory nature—witness the accelerated blood sedimentation and occasional arthritic complications Its manifold generalized manifestations—especially in regard to the saliva, tear and sweat producing glands and the

glands of the gastro intestinal canal—suggest some derangement of the vegetative nervous system Some of the patients are of neuro pathic type

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[1] After *Brit Journal D m l* 1939 51 132

of January, 1938, after which she had practically none When the patient left hospital on May 21, 1938, her general condition had greatly improved, she had gained considerably in weight the anæmia was slighter, and the erythrocyte sedimentation rate was less accelerated After that the improvement continued, but by X ray examination (December 3 1938) there was still gross lung



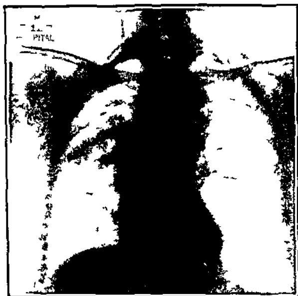
Skiagram of thorax September 17 1937

shadows though they had diminished The right lung had become somewhat contracted and the diagnosis of chronic pulmonary tuberculosis suggested itself though tubercle bacilli had never been found in the scanty sputum and the Pirquet cuti reaction was only normally positive for adults The blood serum gave negative Wassermann and Meinicke reactions The patient had one child (the only pregnancy) said to be living and healthy and grown up The menopause occurred in September 1936

The most puzzling feature in the case had however been the appearance, in all four limbs of tense subcutaneous swellings, which travelled slowly distalwards and then disappeared At the beginning there were pain tenderness and redness of the skin accompanying the swellings the appearance of which was also

preceded by local pain, but otherwise pain and redness were not striking features The swellings were mainly in the subcutaneous tissue but in places seemed adherent to the cutis and the fascia and even the muscle at one part (right biceps) seemed to be involved as if there were some actual myositis The sequence of events (all of which took place under our eyes in hospital) was as follows

About October 21, 1937 a tense swelling with the overlying skin for a time very red was observed in the bend of the left elbow, about the insertion of the biceps muscle and partly in the upper part of the forearm It had been preceded by an aching pain which started suddenly two days previously By November 16 the swelling no



Sk agram of thorax December 3 1938

longer acute divided into two cherry sized nodules had travelled distalwards down the forearm one of these nodules was over the flexor surface of the radius about half way between the elbow joint and wrist whilst the other was over the extensor surface of the ulna, slightly closer to the elbow joint than the wrist There was also a smaller (lentil sized) nodule near the first of these two—a kind of satellite By November 24 the two chief nodules had migrated gradually towards the wrist the skin over them was red they were

not tender, but ached slightly The swellings travelled slowly down towards the wrist and finally disappeared

On December 27 there was considerable swelling (without much pain or tenderness) in the belly of the right biceps, this had begun gradually with local pain on December 23 (There was no blood eosinophilia to suggest trichinosis) By December 30 the swelling in the biceps muscle had completely disappeared, but there was a walnut sized swelling in the position of the right supra trochlear lymph gland very slightly tender to pressure and associated with a little aching pain This swelling increased, and by January 10 1938, had resolved itself into two or three distinct nodules, but by January 20 it was represented only by two nodules slowly travelling down the right forearm as the nodules in the left forearm had done towards the wrist By about February 8 they had both faded away

On January 13 1938 a painful and tender subcutaneous swelling was observed on the inner side of each thigh just proximal to the knee This disappeared, but about January 26 there were pain and tenderness in both calves and on the following day there was swelling at the outer side of both ankles Two days later we observed some oedema of both ankles and of the dorsum of both feet There was still a little pain in the calves, but no tenderness to ordinary touch On February 2 an ill defined subcutaneous swelling could be felt at the back of the lower part of the left calf but both legs seemed well again soon afterwards

In the early part of March there was temporarily an almost painless movable subcutaneous nodule at the ulnar side of the right forearm, close to the wrist over the nodule the skin was slightly reddish This seems really to have been connected with one of the nodules in the right forearm which I thought had disappeared in February Afterwards there was no return of any subcutaneous nodule or diffuse swelling

The patient left the hospital on May 21 1938 but was seen again occasionally feeling fairly well and able to get about On May 11 1939 Dr F G Chandler kindly examined her at St Bartholomew s Hospital and likewise examined all the skiagrams of the thorax that had been taken He did not think the pulmonary condition was tuberculosis but cautiously suggested sarcoidosis On December 19 1939 the patient was feeling very well excepting for some pains She had no cough and had gained in body weight Blood count (May 15 1939) Hæmoglobin 79 per cent, erythrocytes 4,100 000 colour index = 0 96 leucocytes 9 500

On June 12, 1941 she told me that for the last year she had been suffering from a mysterious disease of the left eye A fresh skiagram (June 12 1941) of the thorax showed considerable remaining patches of shadowing Our radiologist Dr E J H Roth thought that the appearances were not those of tuberculosis In regard to the eye trouble she had consulted Mr N Bishop Harman by whose kindness and that of Mr P McGregor Moffatt I was informed that



Skiagram of thorax June 12 1941

there were the signs of severe chronic irido cyclitis but no evidence as to the cause of the attack She was afterwards treated at Moorfields Eye Hospital By April 1942 she was practically blind in both eyes (leucomatous changes) Dr G Markus found that entropion was a complicating factor In addition she had developed a kind of nephritis or nephrosis with 14 per mille albumen in the urine by Esbach s tube

Treatment including fairly large doses of potassium iodide seemed not definitely to help her I hear that she finally died at Brighton about January, 1945 and the cause of death was given on the death certificate a nephritis

As to the remarkable wandering subcutaneous swellings on her limbs at an early period of the disease (1937 38) I have never seen anything similar As they did not ulcerate or form abscesses no culture was made, e g for sporothrix The changes in the lungs, eyes and kidneys were equally puzzling Was the whole illness a form of sarcoidosis or was it sporotrichosis (as had been suggested by Dr K Blum) or a mysterious mycosis (? aspergillosis) of some kind? Lymphangitic swellings and nodules on the limbs are well known in sporotrichosis but in the present patient it is remarkable that the swellings and nodules should have travelled *centrifugally down* the limbs Sporotrichosis may affect the lungs kidneys (pyelonephritis) and eyes (sporotrichic panophthalmia conjunctivitis and blepharitis) *If the present case were originally one of primary pulmonary* and systemic sporotrichosis one might understand a (sporotrichic) lymphangitis spreading from the trunk centrifugally down the limbs Iodides were perhaps commenced too late in the disease

DYSPLASIAS AND DYSTROPHIES OF THE SUBCUTANEOUS TISSUE (Including the Panniculus Adiposus)[1]

Amongst the dysplasias one may include hyperplasias and hypoplasias or aplasias Amongst the dystrophies one may include hypertrophies and hypotrophies or atrophies I limit the term dysplasia as far as possible to include only obviously inborn developmental conditions and processes Generalized obesity and generalized emaciation include respectively hypertrophy and hypotrophy of the panniculus adiposus In some elderly persons the senile involutionary hypotrophic processes show themselves more obviously or earlier in the skin and subcutaneous tissue than elsewhere

The most striking example of limited atrophy of the panniculus adiposus is furnished by the now well known condition (almost always bilateral and symmetrical) termed lipodystrophia progressiva superior which however is not always progressive indeed in some cases the face and neck may remain the only parts of the body involved In the most typical examples in women the atrophy of the subcutaneous fat over the upper part of the body is accompanied by an increase of the fat over the buttocks and thighs, which makes the lipodystrophia more striking by contrast occasionally it may constitute the main feature of the case (*See also* p 113)

In some cases of Cushing s syndrome (especially in women) obesity of the abdomen and trunk may be accompanied by a remarkable thinness of the legs so that one is almost justified in speaking of a lipodystrophia progressiva inferior A lesser degree of disappearance of the subcutaneous fat in the legs below the knees is often present in healthy middle aged women and cannot be termed abnormal In aged arteriosclerotic subjects the dystrophic wasting of subcutaneous tissue may be associated with pruritus and recurrent erythematous or purpuric eruptions of the skin over some limited area similar to local neurodermatitis In a few cases of Cushing s syndrome local symmetrical dystrophic conditions of the subcutaneous tissue may be associated with similar erythematous or purpuric eruptions and generalized diminution of resistance towards pyogenic infections

[1]After *Med Press and Circ* 1943 209 203 205

The condition known as erythrocyanosis crurum frigida puellarum (feminarum) may occasionally include the subcutaneous tissue in the swelling There may, however, be a true chilblainy element superadded

Symmetrical diffuse lipomatosis (so called) of the nape of the neck, and sometimes in front of the axillæ and in other regions, is a form of constitutional localized dystrophic hypertrophy of the panniculus adiposus which occurs in middle aged men—hardly ever in women—who often show a tendency to put on fat to a lesser degree elsewhere They are mostly excessive beer drinkers taking gin or other spirits in addition If they become emaciated from hepatic cirrhosis and ascites (repeated tappings) the symmetrical *deposits do not atrophy to the same extent as the subcutaneous fat* of the rest of the body The condition has apparently become very rare Multiple subcutaneous lipomata are most frequent in the involutionary dystrophic period of life So called adiposis dolorosa (Dercum s disease)—a rare condition seen chiefly in women of the same period of life—is probably at least partly of endocrine origin Patches of (ischæmic) inflammatory sclerosis which may be painful and tender on pressure are not rare in diffuse lipomatosis and Dercum s disease and hypothyroid (endocrine) obesity in women —constituting one form of chronic panniculitis

Areas of dysplastic hypoplasia or of hyperplasia of the subcutaneous tissue and panniculus adiposus of congenital or developmental origin constitute a rare kind of nævus in the broad sense of the term A linear dystrophy of the subcutaneous tissue with local more or less complete atrophy of the panniculus adiposus constitutes a striking form of linear morphœic sclerodermia This rather disfiguring condition (generally affecting only one of the limbs) after progressing for a variable period may remain stationary for the rest of the patient s life In typical linear morphœic sclerodermia the cutis of the whole stripe may become closely adherent to the underlying fascia and muscle as after a Condoleon operation I have seen such a process along the thigh of a woman result in a deep, permanent longitudinal furrow between lofty walls of abundant middle age panniculus adiposus Stripes of this kind bear a striking resemblance to some congenital or developmental linear nævi and one cannot help thinking that some linear morphœic cases arising in early life may really be of the nature of delayed nævi

Atrophic changes in the subcutaneous tissue and panniculus adiposus may accompany variously situated areas of morphœic

sclerodermia Similar atrophic changes, obviously of the same nature, may occur very rarely without actual changes in the skin that can be termed sclerodermatous Small local patches of subcutaneous fat atrophy resulting (as an idiosyncratic reaction) from insulin injections may simulate the (above mentioned) patches allied to morphœic sclerodermia More or less permanent patches of atrophy of the panniculus adiposus result from 'relapsing febrile non suppurative panniculitis, a rare disease or syndrome which has been termed the 'Weber Christian disease

In the well known dystrophic changes at the lower part of the leg connected with varicose veins the subcutaneous tissue may be involved as well as the cutis The cutis may thus become bound down to the periosteum and fascia, and the resulting sclerotic area may then closely simulate the appearance of true sclerodermia In a recent patient there was likewise œdema from myocardial incompetence which naturally could not involve the hide bound area The contrast between this sclerotic area at the lower part of the leg and the œdematous proximal portion of the limb constituted at first sight a puzzling phenomenon Pseudo sclerodermic conditions may perhaps sometimes be caused by deficiency of vitamins (?nicotinic acid) *see* R B McMillan, *Brit Med Journ* 1943, 2 229

In the symmetrical and more or less generalized cases of sclerodermia and dermatomyositis the subcutaneous tissue (with the panniculus adiposus) of the affected areas, particularly of the extremities is to a greater or lesser degree involved This applies to the rarer acute and subacute (true dermatomyositic) as well as to the less uncommon chronic cases It is in the more acute (dermatomyositic) types with much swelling at the commencement that recovery is more likely to take place if the patient survives the active stage of the disease The rare severe acute cases (apparently an infective febrile inflammatory d ease) seem to have a relation to the chronic cases superficially resembling that of the subcutaneous nodules of acute rheumatism and chorea minor to the subcutaneous nodules of rheumatoid arthritis but this analogy will not bear stretching Sclerodermia of sclerodactylia distribution, as in adult cases may arise occasionally even in early childhood In one case it seemed to have already started at or before birth

In sclerodermia and allied conditions such as so called acrodermatitis atrophicans chronica subcutaneous fibrous nodules in

appearance recalling rheumatic nodules, have occasionally been noted—in children as well as in adults

The subcutaneous tissue may, of course be involved in atropho dermias and dystrophodermias of various types including the well known senile or pre senile parchment like areas on the backs of the hands also in rare chronic arterial ischæmic conditions including chronic thrombo angiitis obliterans

In most typical cases of acromegaly hypertrophy of parts of the subcutaneous tissue constitutes a conspicuous feature, notably in the face hands and feet The excessive production of growth hormone in the anterior part of the pituitary gland, which is the cause of acromegaly, seems to work differently in different acro megalics—in some the changes are mainly in the bony skeleton in others the soft parts are equally or even more strikingly affected the viscera may be specially enlarged (acromegalic cardiomegaly gastro megaly etc) and in very few the scalp may be so hypertrophied in area as well as in thickness that it has to become folded or convoluted to keep attached to the skull Thus acromegaly is one cause of the rare clinical condition known as cutis verticis gyrata cutis sulcata capitis furrowed scalp bulldog scalp whirlpool scalp and megalia cutis capitis other causes being a congenital or develop mental nævoid dystrophy and extremely rarely, Recklinghausen s neurofibromatosis (*see* later on) It seems that there are local con stitutional predispositions which determine the relative degree and distribution of the changes due to the growth hormone of acromegaly In very rare cases the distribution is more or less unilateral, one side of the body being more affected than the other Thus in one acromegalic man only the right half of the scalp was furrowed in the above manner (*see* Weber and Atkinson, *Brit Journ Derm* 1928 40 454) I know of one slightly acromegalic woman in whom the dystrophic hypertrophy of subcutaneous tissue is specially marked in the legs and i accompanied by varicose veins There is practically no pitting on pressure but the swelling in the legs is said to become slightly less on lying down The appearance of the limbs suggests a kind of early elephantiasis nostras For a somewhat similar case of chronic elephantiasis like œdema—but of unilateral distribution—in a young woman aged 21 years compare L Lichtwitz *Functional Pathology* 1942 p 75 figs 16 and 17

In Recklinghausen s neurofibromatosis apart from the ordinary characteristic symptoms some cases show remarkable dysplastic

hypertrophic changes in parts of the subcutaneous tissue This may take the form of tumour like masses of connective tissue—with or without special neurofibromatous cords or so called plexiform neuroma —which distend the skin and weigh it down so as to form pendulous tumours in various positions In other cases large areas of hypertrophic and dystrophic subcutaneous tissue and cutis become folded and then hang (dermatolysis) like curtains or flounces about some portion of the trunk or are suspended from the abdomen or lower part of the trunk over the thighs

On 'chalasodermia loose skin dermatolysis and hyperelastic skin compare F P Weber, *Urologic and Cutaneous Review*, 1923 27 407 It is certain that examples of folded hypertrophic (or hyper plastic) skin and subcutaneous tissue cannot all be included under acromegaly neurofibromatosis and nævoid conditions some are connected with pseudo xanthoma elasticum (*see* further on)

The Ehlers Danlos syndrome is due to a peculiar inborn dysplasia mainly of the skin and subcutaneous tissues, whether or not any history of the disease in other members of the family can be obtained The loose skin or cutis laxa is not a striking feature in every case and when present, may be limited to certain parts of the body notably about the elbows and knees The minute tense cyst like spherules which may be felt freely movable in the subcutaneous tissue of a few cases (*see* Weber and Aitken *Lancet* 1938 **I** 198 and *Proc Roy Soc Med* 1938, **31**, 553) are almost completely separated lobules of fat (hence their remarkably free mobility) and obviously represent the result of a peculiar developmental dysplasia of the panniculus adiposus The loose skin or cutis laxa of the Ehlers Danlos syndrome should be distinguished from the so called cutis laxa and folds and flounces of Recklinghausen s disease (*see* above) Moreover in the Ehlers Danlos syndrome the loose skin tends to be specially well marked about the elbows and knees which is not so in neurofibromatosis

It seems that in cutis laxa as in hyperelastic skin (cutis hyper elastica) an atrophic or developmental dysplastic change produces deficiency of the normal attachment of the skin to the deeper structures But microscopical descriptions are not all in accord It is possible that there are varieties intermediate between cutis laxa and cutis hyperelastica and the difference between these two con ditions may depend on the elastic fibres i e on whether they are normal or exaggerated in typical hyperelastic cases and deficient or

dysplastic or dystrophic in typical cutis laxa Thus areas of 'cutis laxa may likewise be present in the developmental dysplastic disease termed by Bock elastosis dystrophica ('pseudo xanthoma elasticum'), which more correctly should be named elastosis dysplastica (*Proc Roy Soc Med*, 1936, **29**, 294 and 1937, **30** 199 Bock *Zeitschr Augenh*, 1938, **95**, 1 W Freudenthal, *Handb der Haut und Geschlectskrankh* 1932 4 part 3 475)

That there is a local dystrophic state connected with so called calcinosis of the cutis and subcutaneous tissue seems evident, but in very rare cases a remarkable feature must be mentioned namely the formation in the subcutaneous tissue over certain areas of a kind of 'lymph sacs reservoirs or cushions which fluctuate like water beds when pressed on This condition of lymph sacs may, perhaps also occur without calcinosis (*see* Atkinson and Weber, *Brit Journ Derm* 1938 **50** 270 J H Sheldon *Proc Roy Soc Med* 1934, **27**, 623 Kunitzky and Melchior, *Arch f Derm u Syph* 1916, **123** 133)

The subcutaneous tissue may, of course be involved in Dupuytren's contraction and in analogous nodular changes in the palms without actual contraction and in acquired or congenital camptodactylia of fingers mostly the little fingers

Some fibrous and fatty and vascular (blood and lymph vessels) lumps and thickenings (single or multiple) in the subcutaneous *tissue and cutis should obviously be regarded as pseudo tumours* of dysplastic developmental origin—hamartomata in E Albrecht's sense of the term—whilst others may be associated not with an *evolutionary dysplasia* but with an *involutionary dystrophic* process of later periods of life e g little telangiectatic venous nodules of lips and mouth in elderly persons plexiform neuroma (plexiform neurofibroma) *and molluscous fibromata and other so called* tumours of Recklinghausen's disease (*see* above) are also hamartomata Here should also be mentioned the local congenital or developmental lymphangiectatic conditions involving the subcutaneous tissue and cutis including cystic and still rarer, lymphorrhagic varieties

I have once seen what I regarded as a peculiar nodular dysplastic condition of the subcutaneous tissue of an emaciated child associated with multiple other abnormalities In rare cases of *true gigantism* of parts of the hands or feet there may be local immense increase of fat associated with thickened cutis and increase of the

fibrous portion of nerve trunks (conclusions from data about a case given me by Dr R A Rowlands, 1931) I do not know whether this condition is allied to what was formerly termed 'malignant lipoma' of a hand or a foot—which, I gather, was not a true neoplasm The elephantiasis telangiectodes of Virchow is according to Virchow, a congenital nævoid vascular condition with secondary hyperplastic thickening of connective tissue elements due to over nutrition from excessive blood supply

Myxœdema manifests itself mainly as a mucinous infiltration of the cutis and subcutaneous tissue, due to hypothyroidism The sub cutaneous tissue as well as the cutis may be involved in rare cases of atypical local *amyloidosis* and probably also to some extent in atypical generalized or 'primary' amyloidosis, with or without special involvement of the tongue (amyloid macroglossia the Lubarsch Pick syndrome)

The subcutaneous tissue may be affected by the nervous system and apparently the Morvan type of syringomyelia may be the cause of Ainhum like changes in persons who have never been in tropical or sub tropical countries

Chronic obstructive œdema from various causes leads to per manent thickening of the subcutaneous tissue of the affected parts and ultimately to a condition of elephantiasis of which condition tropical filarial elephantiasis is the most characteristic example Cases of elephantiasis nostras (i e non tropical elephantiasis) are due to chronic obstructions of veins and lymphatics draining the affected parts owing to venous thrombosis syphilis tuberculosis neoplasms and chronic or recurrent lymphangitis of all kinds The idiopathic œdema of the Nonne Milroy Meige type in which there is often a heredo familial history is due to some unknown con genital or developmental abnormality of the lymphatic circulation of the affected parts This œdema is generally limited to segments of the limbs ('segmental œdema') the segments affected not being necessarily the same in different members of the same family A late developmental œdema apparently of similar nature but almost always symmetrical and frequently without any marked familial incidence which gradually affects the lower limbs of young persons—nearly always females commencing at about 12 to 22 years of age—is unfortunately frequently confused with com mencing œdema of cardiac or renal origin The patients go from one doctor to another and are treated in vain by drugs of the digitalis

and salyrgan classes even operations like that of Condoleon have been tried Rest in bed temporarily removes the swelling completely, at all events during the early stages The patients should content themselves with the use of bandages and, when necessary, lying down For some reason or other the term 'lymphœdema præcox has been introduced for œdema of this class, though every œdema is lymphœdema and, as a developmental œdema, it is rather late in onset than 'præcox Here one may note that the resistance of the tissues towards 'postural (hypostatic) œdema of limbs obviously varies in different individuals and at different periods of life Note also the senile or presenile condition of bags below the eyes

A fœtal type of elephantiasis like universal œdema is one of the phenomena connected with fœtal erythroblastosis, which is now known to be due to a difference between the maternal and fœtal blood in regard to the Rh factor

This concise summary or survey (in which I must admit I have occasionally for reasons of clinical diagnosis alluded also to inflammatory conditions) might serve as a preliminary step towards a monograph on Cutaneous and Subcutaneous Nodules and Nodular Conditions —a vast subject of considerable importance especially in these days of biopsy diagnosis Even if one were to exclude neoplastic metastases the list would be of enormous length—as one would have to include enlargements of the superficial lymph glands

THE NODULES AND LYMPH-GLAND ENLARGEMENT IN RHEUMATOID ARTHRITIS

Also a Syndrome of Rheumatoid Arthritis combined with Multiple Xanthomatous Connective Tissue Infiltrations[1]

In this paper I shall consider the nodules of rheumatoid arthritis and some of the clinical features of cases in which they occur including the occasional moderate painless enlargement of superficial lymph glands

Collins (1937) and others have shown that the characteristic subcutaneous nodules consist of foci of fibrinoid degeneration and necrosis surrounded by a border of tissue reaction, notably by a palisade like radiate arrangement of fibroblasts Obviously such a microscopic appearance cannot be absolutely pathognomonic—showing as it does a primitive type of reaction towards a central degenerative or necrotic core of unknown causation the whole process perhaps commencing as an acute focal exudative lesion Indeed, similar appearances have been described in granuloma annulare and Dr W Freudenthal has shown me microscopic sections in illustration though granuloma annulare is clearly a condition of totally different nature No exact aetiological explanation of the nodules will be possible before the main causative agent of the rheumatoid disease has been discovered

The identity of rheumatic fever with rheumatoid arthritis cannot be proved by any histological resemblance between such primitive types of reactive lesions as Aschoff bodies and the relatively transitory rheumatic nodules in children suffering from rheumatic fever and chorea on the one hand and on the other the nodules of rheumatoid arthritis It is now universally acknowledged that various pathogenic agents (living or not living) may produce the same reactive or degenerative macroscopic or microscopic picture also that a resulting lesion may largely depend on and morphologically vary according to the reactive qualities of the soil on which an identical agent works It must be admitted on the clinical side that

[1]After *Annals of the Rheumatic Disease* London 1944 4 3

I understand that microscopically the so called lipoid necrobiosis (not confined to diabetics) is a somewhat analogous necrotic lesion but containing lipoid

and salyrgan classes even operations like that of Condoléon have been tried Rest in bed temporarily removes the swelling completely, at all events during the early stages The patients should content themselves with the use of bandages and, when necessary lying down For some reason or other the term lymphœdema præcox has been introduced for œdema of this class though every œdema is lymphœdema and, as a developmental œdema, it is rather late in onset than præcox ' Here one may note that the resistance of the tissues towards postural (hypostatic) œdema of limbs obviously varies in different individuals and at different periods of life Note also the senile or presenile condition of 'bags below the eyes

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nodules about affected joints Large lobulated ones at the elbows are connected with the olecranon bursæ Small ones over knuckles of fingers and toes and over both patellæ These latter which developed rapidly and almost painlessly within the last weeks feel like tense cysts and are not definitely attached either to the cutis or to the periosteum There is a large, fluctuating, ganglion like swelling at the back of the right wrist from which there are hernia like protrusions Blood count Hb 58 per cent, erythrocytes 3 900,000 per c mm, C I = 0 73 leucocytes 10 400 per c mm (polymorphonuclears 58 per cent, lymphocytes 31 per cent mono cytes 5 per cent eosinophils 5 per cent, basophils 1 per cent) Blood Wassermann reaction negative Urine nothing special Brachial blood pressure 150/90 mm Hg Blood cholesterol 220 mg per 100 c cm Blood urea 30 5 mg per 100 c cm Blood uric acid 4 1 mg per 100 c cm Basal metabolic rate +10 There is moderate painless enlargement of lymphatic glands in both axillæ No enlarge ment of liver or spleen Some pyorrhœa alveolaris Nothing else of importance by ordinary examination Recent dietetic treatment for gastric ulcer has been successful

Biopsy —My colleague Mr H Rast kindly excised the whole of the subcutaneous enlarged lobulated left olecranon bursal mass in which there was only a minute synovial cavity left The bursa was transformed into a mass of small hard nodules one of which was so superficial as actually to be in the cutis The mass was elongated, measuring 6 5 cm in length, 3 5 cm in width and 2 cm in depth and on incision presented an anæmic whitish, somewhat gelatinous appearance Following is Dr J G Greenfield's histo logical report The central core of the tissue consists of a structure less unnucleated—i e necrotic—tissue which in van Gieson sec tions shows a varying amount of collagen In some places it forms a loose network, in other thicker strands The outlines of old obliterated blood vessels can also be recognized Round this core there is a dense wall of viable collagen (i e nucleated connective tissue with thick collagen fibres) with a palisaded zone of radially arranged fibroblasts between the viable and necrotic tissue In one place early necrosis is taking place here and there are many degenerated neutrophil leucocytes as well as a smaller number of coarsely granular eosinophils Lymphocyte and plasma cell infil tration is present in the lymphatics of the dermis No giant cells seen The photomicrographs show a necrotic centre with radiate reactive border of the rheumatoid arthritis type

there are subacute or chronic cases of rheumatic fever in adults especially those affecting mainly the small joints of the hands, which —for a time at least—very much recall the clinical features of *rheumatoid arthritis and in which the differential diagnosis may* be at first difficult For the matter of that it is not always so very easy clinically to differentiate osteo arthritis (degenerative arthritis) from rheumatoid arthritis Certainly pathological changes of both categories may occur in the same patient, as would seem *a priori* probable Indeed, one would think that a patient with chronic rheumatoid arthritis is more likely than others to develop some of the degenerative changes of osteo arthritis, and vice versa I do not know, however of any case in which a patient with osteo arthritis unmixed with rheumatoid arthritis has developed subcutaneous nodules (of the rheumatoid arthritis type) or moderate painless enlargement of superficial lymphatic glands (of the rheumatoid arthritis type—*see* further on) It is said, indeed, that the very rare *large* type of bone cyst above the acetabulum has been found in osteo arthritis as well as in rheumatoid arthritis Thus Burt (1942) illustrates an example in rheumatoid arthritis whilst Alexis Thomson (1909) figured similar cysts as from a case of osteo arthritis Of great importance is the fact that patients with symptoms (for a time at least) more or less clinically like those of rheumatoid arthritis may present nodules and juxta articular infiltrations which on microscopic examination are found not to conform to the rheumatoid arthritis type But to this subject I will return further on

Some Case Histories

I have mainly selected rather exaggerated examples in which in addition to ordinary changes of chronic rheumatoid arthritis here were subcutaneous nodules—in one case a smaller nodule more cutaneous than subcutaneous could be examined by biopsy—enlarged synovial bursæ with thickened walls ganglia of the hands or wrists, juxta articular thickenings of tendon insertions or tendon sheaths, and moderate painless enlargement of superficial lymphatic glands

Case I

Mrs A B aged 56 years has had rheumatoid arthritis for 25 years The chief changes are in the hands and wrists Large wrist ganglia Lesser changes in the feet elbows and knees Subcutaneous

special Erythrocyte sedimentation rate greatly accelerated Blood Wassermann and Kahn reactions negative The blood cholesterol is rather on the low side The teeth were all removed at least twelve years ago About that time the patient was found to have a duodenal ulcer (confirmed by X ray examination)

Biopsy—Microscopic examination of one of the nodules shows connective tissue reaction with foci of fibrinoid degeneration and



Case 2 Photomicrog aph of a ection f om a sub cutaneous nodule sho ng typical necrotic focus ith rad ate fibrobla tic border

necrosis surrounded by palisade like radiate borders of fibroblasts, as described by Collins (1937) in regard to the subcutaneous nodules of rheumatoid arthritis

CASE 3

E F aged 59 years English A stonemason working at present as a post office packer Rheumatoid arthritis of at least five years

CASE 2

C D, aged 48½ years An office clerk (Weber, 1943, Case 2) Rheumatoid arthritis of three years duration Large cutaneous subcutaneous nodules about the joints, with juxta articular infiltra tions in the tendon sheaths and fibrous structures about the feet, ankles hands, wrists elbows, and knees Most striking are the red shiny nodules over the metacarpo phalangeal articulations and about the elbows—up to the size of large cherries The knees



Case 2 Photograph of nodules on upper limbs July 1945

ankles and feet are similarly affected but the nodules are less red Very characteristic are the nodules along the ridge of the ulna of both forearms from elbow to wrist Moderate painless enlargement of the inguinal, axillary and supracondylar lymphatic glands No obvious splenomegaly None of the nodules are really painful or tender The tendon sheaths at various parts are infiltrated notably in the palms and at the heels (Achilles tendons) The distribution of the nodules and infiltrations is markedly symmetrical There is some stiffness at the back of the neck and owing to the condition of the knees the patient cannot bend forward properly The hands are stiff and show some subluxation of joints The fingers are said to turn dark blue nearly every morning in cold weather Ordinary examination of the thorax abdomen and urine shows nothing

of focal collections of lymphocytes But if one looks at their illustrations (for instance p 147, fig 4 p 169 fig 3 and Plate VIII) one recognizes the presence in these focal collections of so called germ centres of Flemming Now surely such lymphadenoid foci with typical germ centres can hardly be considered as pathognomonic of any special disease Apart from their conspicuous presence in normal lymphadenoid tissue (lymph glands tonsils the walls of the vermiform appendix and intestines the Malpighian corpuscles of the spleen), they form a special feature in so called lymphadenoid goitres and are also not rare in thyroids from patients with Graves disease I have seen them in abnormal salivary glands They constitute a conspicuous feature of cutaneous lymphocytomata (Epstein 1935) and may be found in various other pathological conditions

The Painless Lymphadenopathy

Neither is there anything absolutely pathognomonic in the painless lymphadenopathy of the superficial lymph glands which is present in many cases of rheumatoid arthritis though seldom noticed by the patients themselves and often not looked for by the examining doctor I myself have had a biopsy in only one of my cases but I believe that the finding is typical for other cases also— namely, a non specific follicular lymphadenopathy of toxic or infective origin with marked enlargement of the germ centres of Flemming This must of course not be confused with the early stages of follicular reticulosis or follicular lymphoblastoma of non inflammatory (neoplastic) origin It tends to disappear when the general and articular conditions improve

CASE 4

Mrs G H aged 65 years Of thin wiry build was under treatment in 1941 and 1942 for rheumatoid arthritis She had suffered from lobar pneumonia of the right upper lobe in the spring of 1939 In September 1940 she began to suffer from rheumatoid arthritis afterwards located notably in the hands with some fusiform swelling of the finger joints There was also considerable stiffness of the cervical spine Some moderate discrete painless enlargement of superficial lymph glands in neck axillæ and groins of which patient herself was unaware No enlargement of spleen or liver Brachial blood pressure 190/90 mm Hg Some hypertrophy of the left ventricle of the heart apparently from high blood pressure Trace

duration On the whole however an active man of 'wiry type Hard subcutaneous nodules about the size of an olive over ulnar ridge near either elbow of about six months duration, not painful but slightly tender to pressure Moderate, painless, symmetrical enlargement (the patient was unaware of this) of lymphatic glands in axillæ and groins No *enlargement of spleen or liver* Tense cyst like, pea sized painless nodule over the proximal interphalangeal joint of the right fourth finger, which appeared about twelve months ago suddenly (as patients say such small nodules of rheumatoid arthritis do) This was a cutaneous rather than a sub cutaneous nodule *He* also has moderate flabby enlargement of the right olecranon bursa which hurts slightly if he leans on it Some stiffness and ulnar deviation of the fingers of the right hand Slight stiffness in cervical spine He had other symptoms formerly that disappeared under treatment No history of gonorrhœa or syphilis Nothing special by ordinary examination of thorax abdomen nervous system and urine Slight anæmia Blood sedimentation slightly accelerated Blood Wassermann reaction negative Blood cholesterol 345 mg per 100 c cm Blood calcium 9 mg per 100 c cm Blood urea 43 mg per 100 c cm Blood uric acid 3 2 mg per 100 c cm

Biopsy—My colleague Mr H Rast excised the above men tioned nodule from the knuckle of the right ring finger and it was carefully examined by Dr W Freudenthal It showed multiple foci of so called fibrinoid degeneration and necrosis (as described by Collins 1937) some of them surrounded by a palisaded border of fibroblastic reaction elastic fibres practically absent from the degenerative areas no giant cells seen

Remarks

Even if the histological features of the nodules of rheumatoid arthritis were absolutely pathognomonic one would still be far from the discovery of the essential pathogenic agent of the disease But, as I have already pointed out the type of lesion in question cannot be regarded as really pathognomonic Allison and Ghormley (1931) (compare also Ghormley 1938) made a great point of what they call focal collections of lymphocytes in the synovial membrane of joints being almost pathognomonic of proliferative arthritis of uncertain origin—that is to say of rheumatoid arthritis They write (p 139) Diagnosis made positive on discovery in the tissues

A Syndrome of Rheumatoid Arthritis Combined with Multiple Xanthomatous Connective-Tissue Infiltrations

There are other subcutaneous nodules and infiltrations which might in rare cases be confused with those of rheumatoid arthritis (Weber, 1943), but I shall here confine myself to a condition which seems to be genuine rheumatoid arthritis associated with multiple xanthomatous nodules and infiltrations especially about the joints and in the subcutaneous (occasionally cutaneous) tissue

The special case that I shall fully record here has been under observation for several years I described it originally with Dr W Freudenthal in 1937 and later in 1943 (Weber and Freudenthal, 1937 Weber 1943), but can find no literature on the subject excepting perhaps Layani s case of Xanthomatous chronic deforming rheumatism (Layani, 1939 Layani and others 1939) Layani s case was that of a woman, aged 46 years who had a deforming rheumatoid disease of fifteen years duration In addition to the xanthomatous condition she had prolonged jaundice with hepatomegaly and there were other remarkable features in the account

However, owing to the kindness of Dr George Graham and Dr E T D Fletcher I have been able to examine two other men in England apparently suffering from a somewhat similar syndrome I hope that an account of these two cases will appear in due course As I have been given kind permission to refer to these cases with my own one I will here emphasize the point that hypercholesterolæmia seems not to be an essential and is certainly not a constant symptom Another point is that the infiltrations tend to be greatly in excess of those generally recognized as an occasional feature in typical rheumatoid arthritis In all three cases there was strong evidence that the application of heat made the xanthomatous infiltration worse This was pointed out to me by Dr Graham from various observations in his own case and it may be of some therapeutic significance Dr Fletcher s patient believes that radiant heat therapy (which was given previously to seeing Dr Fletcher) had made his trouble rather worse than better Both my patient and Dr Graham s patient developed a florid increase of the subcutaneous infiltrations—which tended to become actually confluent in parts over their shoulders and backs (the specially hot parts) after they had been lying for days on their backs in bed Another remarkable feature in both Dr Graham s patient and mine was the occurrence

of albumin in the urine Blood count (July 1, 1941) Hb 65 per cent, erythrocytes 3 580 000 per c cm , C I = 0 91, leucocytes 6,150 per c mm (polymorphonuclears 71 per cent, lymphocytes 21 per cent monocytes 6 per cent , eosinophils 1 per cent basophils 1 per cent)

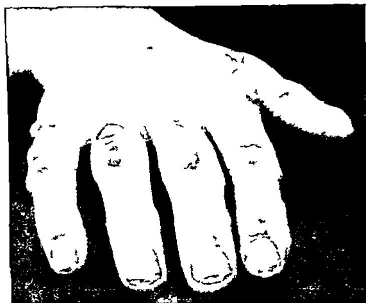
Biopsy —On September 12 1941 Mr Rast excised one of the enlarged lymph glands from the right axilla Dr J G Greenfield's microscopical report is The sections show general proliferative activity with many mitoses in the lymphoid centres and occasional



Case 4 Photomicrograph of a section from an enlarged lymph gland showing toxic or infective follicular lymphadenopathy with large germ-centres

collections of polymorphonuclear cells in relation to the sinusoidal systems There is also a slight fibrosis of the gland These are all evidences of toxic or bacterial stimulation of no specific type

When the patient left the hospital on November 13 1942 she could walk almost normally and no enlargement of any superficial lymph glands could be felt, excepting the inguinal glands and that very slight and on the right side only



Case 5 Photograph of the right hand November 14 1936

C 5 Photograph of the right elbow November 14 1936

(in addition to the large and medium sized nodules) of minute (miliary) superficial nodules ("droplets"), evidently arising in the outer part of the cutis these appeared for a time in great numbers on the nose, forehead and other parts of the face and then disappeared without leaving a trace In my case the ultimate atrophy or involution of the large nodular infiltrations tended to be more complete than that which occurs in acknowledged cases of rheumatoid arthritis Finally I cannot help thinking that the xanthomatous infiltrations in these little known cases may have a relation to the rheumatoid arthritis analogous to that which gouty tophaceous deposits sometimes appear to have to osteo arthritis with exaggerated Heberden s nodes It may be remembered, by the way, that Chauffard and others (1921 and 1923) found that tophaceous deposits contained a considerable admixture of cholesterol In Dr Graham s case a large sarcoma like growth ultimately developed *This reminds me of the possible though doubtless exceedingly rare* relation of sarcoma to benignant so called xantho myeloma of tendon sheaths and perhaps it might also be compared to the very rare supervention of frank spindle celled sarcoma in multiple idiopathic hæmorrhagic sarcoma of Kaposi (which is generally considered not to be a true sarcoma) I well remember this occurring in an old case of Sequeira s (Sequeira and Brain 1906)

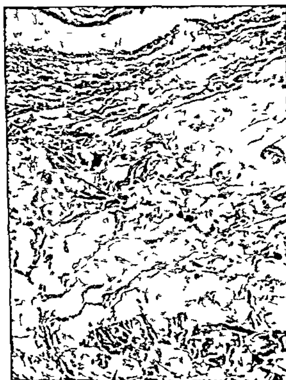
CASE 5

This case was demonstrated by Parkes Weber and Freudenthal at the Royal Society of Medicine in December 1936 (Weber and Freudenthal 1937) under the heading Nodular non diabetic cutaneous xanthomatosis with hypercholesterolæmia but the presence of cholesterol in the lesions was not absolutely proved, and the hypercholesterolæmia was certainly not constant Following is the account of the case up to the time of the demonstration in 1936

K L a man aged 35 general labourer began six months ago to suffer from pains and stiffness in various joints which obliged him to give up work Since then he has had varying swellings of the knee joints and of the tendon sheaths at the back of the wrists now hardly noticeable During the last six months cutaneous nodules (freely movable over the deeper parts) have been appearing on the hands mostly on the back of the fingers and thumbs especially near the joints they are hard and reddish averaging a small pea in size During the same period similar nodules appeared over the ulnar

Blood uric acid 3 7 mg per 100 c cm Non protein nitrogen in the blood 30 5 mg per 100 c cm Blood serum calcium 8 5 mg per 100 c cm Blood-count (November 24) Hb 84 per cent erythrocytes 4 500 000 leucocytes 3 500 per c cm (eosinophils 7 per cent polymorphonuclear neutrophils 45 per cent, lymphocytes 45 per cent, monocytes 3 per cent)

Biopsy —Histological report by Dr W Freudenthal The main change seen in the sections is the presence of large masses of cells



Case 5 Photomicrograph of a section from an excised nodul The epidermis is seen in the upper part of the figure and the larg ize of the prexanthoma c lls *is obvious by omparison with the ie of the ep dermis* cells

which form round or oval more or less defined areas and are scattered irregularly between the bundles of the collagen tissue in all parts of the cutis The cells are so numerous that their mass

ridges up to the size of a cherry over the right olecranon two pieces were excised for biopsy purposes from the left elbow and one pea sized nodule from over the base of the left index finger Numerous smaller nodules are to be seen over the external ears and still smaller ones (really miliary or minute) on the face, especially over the borders of the lips and nostrils Some of the minute facial nodules have a yellowish red colour None of the nodules have been itching or painful or tender to pressure, except the large ones at the elbow Recently in December, fresh nodules, mostly red, have appeared about the elbows over the back of both great trochanters, over the buttocks and over the coccyx in the intergluteal fold There is now also a conglomerate or confluent nodular plaque over the back of both acromial regions—more pronounced on the right side on which the patient usually lies It is highly probable as I stated above that this florid exacerbation of the subcutaneous infiltrations was induced by local heat due to the patient lying for days in bed His body weight is 53 2 kilogrammes, against (apparently) 60 kilogrammes early in November

There is nothing especial in the past history, excepting dysentery in 1920 in India The patient was kindly handed over by Dr M B Ray and he was in hospital under my observation from November 14 1936 to April, 1937

In the hospital there was occasional slight fever in November By ordinary examination of the thorax and abdomen and by X ray examination of the thorax and bones of the hands and feet nothing abnormal is found nor is there anything special to be noted in regard to the nervous system and eyes (fundi normal) and internal parts of the ears nose, and mouth (including pharynx) There is no thickening of the ulnar nerves at the elbows The urine shows nothing abnormal (unless very slight excess of urobilinogen) and no alimentary glycosuria follows the ingestion of 50 g glucose Fasting blood sugar 0 07 per 100 c cm Blood sugar curve normal Blood serum cholesterol on the first occasion was 230 mg per 100 c cm and on the second 350 mg per 100 c cm Fractional examination of the gastric contents shows complete absence of free hydrochloric acid even after a subcutaneous injection of histamine pepsin present The *blood serum which is clear but somewhat over* coloured, gives a negative direct but positive indirect van den Bergh reaction Wassermann and Meinicke reactions negative in the blood Pirquet cuti reaction negative Blood sedimentation not decidedly accelerated Blood urea 36 5 mg per 100 c cm

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Postscript February 1947 —In a medical thesis of 1945 (reviewed in the *Presse Medicale* September 7 1946 p 577) P Rochu points out that the lymphadenopathy associated with what we in England term rheumatoid arthritis together with the arthritis and splenomegaly show that the reticulo endothelial system is obviously involved the disease is much more than a joint disease and the Chauffard Still Felty syndrome cannot be separated from it

matoid disease She is a well built woman of about 10 st 4 lb in weight There is chronic thickening of both wrists with limitation of movement Both elbow joints cannot be properly extended The right knee is somewhat flexed and there is crackling on movement The left knee seems normal There is thickening around the proximal interphalangeal joint of the left little finger and apparently some infiltration of its flexor tendon sheath No other joints are affected, and there are and have been, no cutaneous or subcutaneous nodules She has had twelve children of whom ten are living and well Her rheumatoid troubles commenced in both hands eighteen months after the birth of her third child that is to say, about sixteen and a half years ago She has never had pain in connexion with them she says, except a little aching in rainy weather, and she has never really been laid up It is possible that her condition is similar to that of her brother but a very incomplete form of the disease

Summary

In this paper the nodules infiltrations, and painless adenopathy of rheumatoid arthritis, and their pathological significance, are considered

Attention is also drawn to the existence of a little known syn drome in which clinical features of rheumatoid arthritis are asso ciated with nodules and infiltrations apparently of xanthomatous nature though hypercholesterolæmia seems to be of not necessary (at least not constant) occurrence I have described only one case fully (which was first observed many years ago) but I know of the existence of other cases probably of the same category, two of which will I hope be fully described in due course The interest of this syndrome does not lie in its extreme rarity but rather in the light *which when more completely studied it is likely to throw on* the pathology and nature of various other groups of cases

My thanks are due to Dr George Graham Dr M B Ray, and Dr Ernest T D Fletcher for enabling me to see and helping me to examine some of the patients to Mr H Rast for carrying out the biopsy excisions to Dr W Freudenthal and Dr J G Greenfield for their microscopic reports and to Dr Greenfield for photomicro graphs and to the Editors of the *British Journal of Dermatology* and the *Proceedings of the Royal Society of Medicine* for allowing me to use previous papers of mine and blocks for illustration

V

SOME TELANGIECTATIC AND OTHER ANOMALOUS VASCULAR GROUPS, ESPECIALLY THOSE OF DYSPLASTIC ORIGIN,

including those probably resulting from non-genetic 'accidents' during intra-uterine development[1]

INTRODUCTORY REMARKS

THE following is a rough classification of various telangiectatic and some other anomalous vascular conditions according to their main clinical and pathological features Treatment is not considered For convenience I include fixed local erythemas due to persistent dilatation of the superficial capillaries of the affected parts (telangiectatic erythema) even when the reddening is not accompanied by dilatation of individual vessels sufficient to be visible to naked eye inspection I have for convenience even included the recurrent flushing of a single area known now as Frey s syndrome

In minute macular or papular vascular lesions it is often hard to decide whether the constituent vessels are simply telangiectatic (from local degenerative or inflammatory causes) or are of benign neoplastic or of hamartomatous origin Consequently certain lesions are termed telangiectases or angiomata (hæmangiomata) indiscriminately according to the fancy of the doctor

When telangiectases are due to local yielding of vessel walls of hypostatic, toxic or inflammatory origin it is obvious that they may be occasionally accompanied by true purpura due to diapedesis through the affected vessel walls (for instance purpura annularis telangiectodes of Majocchi purpuric pigmented lichenoid dermatitis and hypostatic dystrophic purpuric and pigmentary conditions) sometimes there may be an avitaminosis factor present

Spiders aggregations of linear telangiectases and local patches of persistent erythema (without obvious naked eye dilatation of individual vessels) when present in children and young persons are probably usually of congenital or developmental dysplastic origin and may be regarded as dysplastic vascular nævi (or delayed nævi) in the broad sense of the term nævus and are allied to hamartomata (Albrecht) They may fade become less evident or altogether disappear for a time when for any reason they are empty of blood

[1] After *Med Press and Circ* 1943 210 219-224

IV

CHRONIC NECROBIOTIC SUBCUTANEOUS NODULES OF THE RHEUMATOID ARTHRITIS TYPE

FOLLOWING is a letter I wrote — *Lancet*, 1944, 2 611 —

Since Collins (1937) and others have conclusively shown that the characteristic subcutaneous nodules of rheumatoid arthritis consist of foci of fibrinoid degeneration and necrosis surrounded by a border of tissue reaction notably with a palisade like radiate arrangement of fibroblasts, it has become evident that not all sub cutaneous nodules in cases of rheumatoid arthritis are micro scopically of exactly the same type (F P Weber *Brit Journ Dermat* 1943, 55 1 and *Ann Rheum Dis* 1944, 4 3) To facilitate further work on the subject (biopsy results especially) I would suggest that the nodules of the now well known type, as described by Collins and others should be termed chronic necrobiotic subcutaneous nodules of the rheumatoid arthritis type, this term to include indurations of similar structure in the walls of bursæ in tendon sheaths and attached to fasciæ, ligaments or periosteum or in a very few cases, *apparently arising from or involving the deep cutis* Some of the exceptional nodules which I have in mind may apparently differ altogether in histological structure whilst certain others may differ only by deposition in the nodule of calcareous or lipoid (cholesterol) or other material I cannot help thinking that further biopsy examinations will furnish us with data of clinical and especially diagnostic value

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[1]*After Med P ss and C* 1943 210 219-224

'Spiders and ruby spots may completely vanish owing to spontaneous involution or blockage of supplying vessels

Telangiectases of congenital or developmental dysplastic origin may be connected with other vascular dysplastic conditions elsewhere Thus, dysplastic developmental aneurysms of the splenic artery have been found associated with hæmorrhagic telangiectasia of the Osler type (Norah Schuster, 1937), which is certainly a developmental dysplasia of the cutaneous and mucosal blood vessels This may also be compared with the fact that dysplastic (supposed 'congenital) developmental aneurysms at the base of the brain have been associated with co arctation (stenosis) of the aortic isthmus (F P Weber, *Proc Roy Soc Med* Section of Medicine, 1927, **20** 29 and 1928 **22** 7 F H K Green *Quart Journ Med*, 1928, **21** 419, Baker and Shelden, *Amer Journ Med Sci*, 1936, **191**, 626)

The most generally known dysplastic vascular abnormalities of the skin are of course the congenital (systematised or not systematised) telangiectatic areas of the port wine stain type (capillary angiomata) and the dysplastic vascular pseudo tumours generally *called venous or cavernous angiomata, such dysplastic pseudo* tumours are, according to my classification, examples of Albrecht s hamartomata But dysplastic vascular abnormalities of the skin may be the reverse of telangiectatic and I think that the mottled pale patches on the thorax or other parts, known as *nævus anæmicus* (Voerner, 1906) are most probably explained as due to local dysplastic vascular deficiency contrasting with the common telan *giectatic red or port wine nævus Both these may be present* in the same individual In regard to their possible relations to the nervous system *see* F P Weber *Brit Journ Derm* 1929 **41** 221 and Weber and Harris, *ibid* 1932 **44** 77

Nature of Næi —Nævi to my mind in the broadest sense of the term, are developmental—mostly congenital—dysplasias The individual lesions are usually small but often multiple Large nævi may *involve whole regions or segments of the body Nævi in more* or less systematized distribution may occupy the surface of almost the whole of one lateral half of the body (nævus unius lateris) and sometimes also considerable portions of the other half as well occasionally the whole surface of the body may be more or less involved in telangiectatic and other dysplastic (hyperplastic or hypoplastic) changes Such extensive nævoid conditions may sometimes be associated with bony or other abnormalities or malformations of development

Classification into Groups

(1) *Ruby spots* called also *De Morgan spots* after the Middlesex Hospital physician should be familiar to all, as every adult and even some children will find one or more on some part of the body if they search for them (F P Weber, *Brit Med Journ* 1936 **2** 693 and *Proc Roy Soc Med*, 1939 **32** 1394) They are apparently true benignant neoplasms (minute capillary angiomata) and although some of them disappear by spontaneous involution (?thrombotic or atrophic closure of the supplying blood vessel) they tend on the whole to increase in number with the individual s age Of course doctors who thought that these spots had some connexion with cancer were confirmed in their opinion by finding them present in all their cancer patients without exception others found them a constant feature in all patients with degenerative heart disease others have found them associated with mental disease and so on But although interesting from this historical point of view they have no significance for any therapeutic or general diagnostic purpose I regard them as simple mutational tumours (rather than telangiectases) of the cutaneous capillaries and of no importance not even as blemishes and hardly as identity marks They may formerly have been of supposed value as witch marks !

(2) *Linear (hair like or branched) telangiectases* occur in most persons at some period of their lives In children and youthful individuals they are doubtless generally of dysplastic origin but in the old they are likely to be connected with (almost normal) degenerative processes On the nose and face they are often present as permanent degenerative results of the frequent flushings of rosacea which may be connected with gastric irritability alcoholic indulgence excessive tea drinking etc When associated with the punctiform telangiectases and spiders of the Osler type of telangiectasia they are of developmental dysplastic origin and often familial In elderly persons as already mentioned they may be regarded as qualitatively if not quantitatively of almost normal (degenerative) occurrence

Those seen in young persons on the back of the root of the neck and between the shoulder blades are of dysplastic nature and have often been thought to constitute a sign of actual (?latent)—or constitutional tendency to—pulmonary tuberculosis but this is altogether false Cf F P Weber Significance of Cervical Capillary Markings *Lancet* 1916 **1** 589

The "telangiectatic girdle around the trunk at about the level of the diaphragm is likewise of dysplastic origin though it may be favoured by bronchitis, asthma, and pulmonary emphysema and *tends to increase with age*

Telangiectatic (as well as pigmentary) changes, notably on the face, are occasionally associated with *sclerodermia*, especially of the symmetrical (sclerodactylia) type They sometimes accompany the allied conditions of *acrodermatitis chronica atrophicans* (*atrophica*) of Herxheimer and *erythromelia* of Pick Fine telangiectases may be present, with redness especially on the eyelids and face, in subacute *dermatomyositis* or *poikilodermatomyositis*

Acquired plaques of telangiectases may be idiopathic (Brocq), or may be caused by X rays

(3) *The branching linear telangiectases on the thighs* especially seen in young women, often with a blonde delicate type of skin are of course of dysplastic origin, though with age they often develop into upper femoral superficial *varices* They do not necessarily signify the ultimate development of regular varicose veins of the legs but they sometimes constitute a portion of the rare dysplastic condition which in later life may be termed progressive arborescent dysplastic telangiectasia (*see* further on group 4) Patchy symmetrical telangiectasia of the lower limbs (mostly in women) may be associated with a peculiar *friability* (*low resistance*) *of the skin leading to indolent ulcers* especially about the ankles organic changes in the capillaries arterioles and venules may be present

(4) *Progressive diffuse symmetrical dysplastic arborescent telangiectasia* is a rare condition best marked in the lower limbs of elderly women (compare F P Weber *Proc Roy Soc Med* 1939 32 1394, Mitchell Heggs Wilson and Leitner *ibid* 1396) It may be regarded in some cases as an extreme and progressive form of the preceding telangiectatic dysplasia of the thighs, in which a degenerate factor with increasing years has been added to the developmental dysplastic one The picture of a fully developed case is very striking Allied is perhaps an extremely rare type of *universal telangiectasia with atrophic changes in the skin* but the latter condition is more likely to occur in children as a kind of universal nævus or systematized more or less unilateral nævus (nævus unius lateris) of telangiectatic nature combined with patchy hypoplastic dysplastic appearances in the skin

(5) *Spiders* This is a convenient short American term for what have been described under the headings spider telangiectasis 'spider angioma spider nævus, nævus araneus stellate (star

like) nævus, stellate angioma stellate telangiectasis The 'body of the spider or the centre of the star is the dilated terminal portion of a cutaneous arteriole and the limbs of the spider or rays of the star are the dilated capillaries into which the arteriole breaks up Pulsation of the centre which can be easily felt with the finger in some cases is due to true expansile pulsation of the dilated end of the arteriole with each heart systole or to systolic straightening out of the arteriolar stem if the arteriole is developmentally of a corkscrew or spiral form (F P Weber *Brit Journ Derm* 1938 50 31 with histological examination by Dr W Freudenthal)

Spiders in children and young persons are probably mostly of congenital or developmental dysplastic origin and allied to hamartomatous nævi but they may possibly sometimes (as has been supposed) be associated with a constitutional delicacy of some kind and want of resistance towards infections When arising in older individuals they may be of toxic or local inflammatory or degenerative origin and their frequent association with cirrhosis and hepatic disease is well known When arising during pregnancy they may be possibly of hormonal (œstrogen) origin that is to say the female sexual hormone may be a factor in their causation—*see* Walsh and Becker (*Arch Derm and Syph* 1941 44 616) and W B Bean (*Amer Journ Med Sci* 1942 204 251 and *Amer Heart Journ* 1943, 25 463) who described cases associated with acquired persistent palmar erythema In regard to their connexion with liver disease and chronic infections compare J Galloway s remarkable case *Proc Roy Soc Med* Clin Section 1911 4 42 Spiders constitute an important feature in the Osler type of telangiectasia (group 6)

(6) *Telangiectasia of the Osler type (hereditary hæmorrhagic telangiectasia of the skin and mucous membranes Rendu Osler telangiectasia)* My own earliest contribution to the subject was a paper in 1907 on a typical familial example (*Lancet* 1907 2 160) and in 1924 (*Brit Journ Child Dis* 1924 21 198) I alluded to analogous hæmorrhagic conditions in the alimentary respiratory and urinary tracts The telangiectases in this disease are of the spider linear and punctiform kinds The chief sites are the face and mucous membranes of the lips mouth pharynx and nose but the punctiform telangiectases on the fingers sometimes beneath the nails are very characteristic The mucosa of other parts of the respiratory and alimentary tracts may be involved and hæmoptysis hæmatemesis hæmorrhage from the bowel and hæmaturia occur in rare

cases, but epistaxis is the chief hæmorrhagic symptom and may occur in the absence of *obvious telangiectases of the nasal mucosa*, familial epistaxis probably of the same nature has been described without obvious telangiectases having been noted anywhere In some cases no family history of the disease can be obtained In very rare cases no hæmorrhage occurs In most cases attacks of epistaxis precede the appearance of obvious cutaneous telangiectases, the cutaneous telangiectases most frequently become manifest decidedly after the period of puberty To the present group, it seems to me might belong the patient who developed generalized telangiectasia after measles and whose face is figured by G C Andrews (*Diseases of the Skin*, second edition, 1938 p 803 fig 882) The literature has been exhaustively dealt with by H I Goldstein

The disease is a developmental often definitely hereditary (Mendelian dominant) dysplasia of the minute blood vessels of the skin and mucous membranes but symptoms may arise which are due to secondary anæmia caused by the repeated loss of blood Degenerative changes may be superadded to the dysplastic condition Raynaud like angiospastic attacks have been noted (Wigley and Heggs, 1934) A few cases have been described (Eli Davis 1939) in which simple purpura was associated Various developmental abnormalities have occasionally been noted The spleen has *sometimes been enlarged and in Norah Schuster s case multiple* aneurysms of the splenic artery (? dysplastic developmental) were found at the post mortem examination (*Journ Path and Bact* 1937, 44 29) Lowered blood calcium has also been noted Hepatic cirrhosis has been recorded

Penfold and Lipscomb (*Quart Journ Med* 1943 new series, 12 157) have given a careful account of a Jewish family in London whose members showed hereditary hæmorrhagic telangiectasia combined with the developmental abnormality of the red blood cells known as (human) *elliptocytosis*

(7) *Patches of persistent erythema on the soles palms face or elsewhere* are quite different from the patches of fixed erythema occasionally caused by the use of phenolphthalein or certain other drugs I have little doubt *that some cases are really of dysplastic* origin and may be regarded as patches of congenital or developmental *erythrokeratosis without the keratotic component* J E Lane s two cases of *erythema palmare hereditarium* (*Arch Derm and Syph* 1929 20 445) and similar erythema of palms and soles are due to genetic local capillary abnormality In this connexion one

may call to mind the *luedo like* (*luedoid*) *telangiectatic patches* occasionally met with on various parts of the body or limbs and which are either telangiectatic nævi of slight degree (*i e* relatively pale) or represent the remnant of ordinary telangiectatic nævi which have incompletely involuted Telangiectatic patches occur in the sacral region in some cases of spina bifida (with or without local pigmentation) Some mentally defective children have symmetrical red patches on the face (cheeks)

Cases of acquired persistent erythema palmare associated with spiders have been described by Walsh and Becker and by W B Bean as I have already mentioned Walsh and Becker were apparently the first to direct attention to a connexion with pregnancy

Patches of persistent infiltrated cutaneous erythema are sometimes met with on the face especially forehead of middle aged men with *hypertonia polycythæmica* (polycythæmia hypertonica the Geisbock or hyperpiesic type of polycythæmia) In some cases at all events these patches seem to be only modified rosacea in erythræmic subjects

(8) *Angiokeratomata* (*telangiectatic keratoses*) and more diffuse *angio keratotic cond tions* are perhaps partly of dysplastic origin Those on the scrotum and penis and on the body are little hyperkeratotic nodules on telangiectatic or angiomatous bases like small vascular nævi They or their hyperkeratotic constituent may spontaneously disappear more or less completely The rare angiokeratomata (Mibelli) on the fingers (more rarely feet or ears or nose) mostly in young persons are sometimes connected in some way with a chil blainy type of circulation

(9) *Congenital varicose veins* This is a local dysplastic dilatation and thickening of veins (phlebectasis) of any portion of the body allied to hamartomatous changes It is a kind of local venous gi gantism superficially analogous in the alimentary tract to congenital megalocolon (Hirschsprung s disease) The ordinary recognized causes of varicose veins are not present Arteries may also be involved (phlebarteriectasis) Compare F P Weber *Brit Journ Child Dis* 1918 15 13 and 1936 33 102

(10) *Hæmangiectatic hyp r rophy of limbs* Many years ago I grouped together various mostly unilateral conditions under this heading (in which the affected limb was definitely longer than the unaffected one of the other side) to distinguish them chiefly from the Nonne Milroy Meige congenital or developmental often heredo familial œdema of limbs *See* Parkes Weber *Brit Journ Child Dis*, 1918

15 13 and A M H Gray, *Proc Roy Soc Med*, 1928, 21 65 (with discussion) So called congenital varicose veins may constitute a part of the hæmangiectatic picture in such cases My name has been associated with this condition by A M H Gray and some others, in Argentina it has been termed the Parkes Weber Klippel or Klippel Parkes Weber syndrome (compare P P Reichenheim, *St Barth Hospital Journ* 1943 wartime series 4, 53) Typical cases are always distinguished by increased length of long bones in the affected (usually a lower) extremity, in which there is also obvious enlargement of arteries or veins or both, often there are vascular hamartomata in the affected extremity or other parts of the body, such as not rarely accompany developmental hemi hypertrophy The primary cause of the developmental condition is uncertain, but the enlargement of long bones may be connected with increased arterial blood supply possibly due to increased size of the nutrient artery This condition in my opinion, differs from so called *true gigantism* of hands feet fingers or toes by absence of excessive thickening of the nerves of the affected part, true gigantism being probably usually of the nature of neuromatous or neurofibromatous hypertrophy (neuromatous elephantiasis) and allied to Recklinghausen s neurofibromatosis and so called plexiform neuromata Telangiectatic hypertrophy of limbs is of course a dysplastic condition and is frequently associated with dysplastic anomalies in the skin or other parts There is seldom if ever any evidence of a similar condition in other members of the family

The term *elephantiasis telangiectodes* (Virchow) has been applied to a very rare congenital or developmental dysplastic condition characterized by local thickenings of skin and subcutaneous tissue with great enlargement of blood vessels According to Virchow the elephantiasis like condition is gradually produced by excessive blood supply causing over nutrition of the connective tissue elements The hyperplastic thickenings may cause folds as in the dermatolysis of Recklinghausen s neurofibromatosis I have never seen such a case

(11) *Hæmangiectatic nævoid conditions involving both face and cerebral meninges* I happened to be the first to publish the radiographic appearances of the brain in a typical case of this class with calcification (Parkes Weber *Journ Neurol and Psychopath* 1922 3 134 9 and *Proc Roy Soc Med* 1928 1929 22 431) K H Krabbe (*Arch Neur and Psych* 1934 32 737 55) suggested the term *Parkes Weber Dimitri disease*, and Hilding Bergstrand (*Second Internat Neurol*

Cong 1935 abstracts p 124) called the condition the *Sturge Weber disease*—the name also employed by the Swedish brain surgeon, H Olivekrona W Allen Sturge (*Trans Clin Soc Lond* 1879 12 162 7) reported the case of a girl aged 6½ years with an extensive telangiectatic nævus especially of the right side of the face and head right sided buphthalmus and epileptic fits commencing in the left hand He concluded that the right side of the brain was also involved in the nævoid condition R Schirmer of Greifswald (*Graefe s Arch f Ophth* 1860 7 Part 1 119 21) had already described the case of a man aged 36 years with an extensive telangiectatic nævus especially of the left side of the face and left sided buphthalmus, but he made no allusion to epileptic fits or brain disease I have suggested (*Brit Med Journ*, 1936 1 708) that the disease ought to be called the Sturge Kalischer rather than Sturge Weber disease as the pathologist S Kalischer published the post mortem examination of a case in 1901 Dr K Blum has suggested the name Sturge Kalischer Weber disease

In this dysplastic hamartomatous disease a more or less wide spread vascular nævus of trigeminal or more extensive distribution on one side of the face is associated with a vascular leptomeningeal nævus (plexiform angioma) on the same side Contralateral con vulsive attacks occur and there is usually more or less contralateral hemiparesis with hemihypotrophy (or hemihypoplasia) the limbs and perhaps the face being smaller on the contralateral side Skia grams of the head show a peculiar festooned pattern due to calcifi cation about the blood vessels of the meningeal lesion This calcifi cation however by itself is probably not the cause of the hemiparesis and hemihypotrophy

The condition is developmental and there is seldom (if ever) any evidence of hereditary or familial occurrence It should be compared to Bourneville s disease (tuberous sclerosis epiloia) and Lindau s disease In Lindau s disease which may be familial brain lesions are present not rarely in the cerebellum but never above the tentorium cerebelli as they invariably are in the Sturge Weber disease In the latter disease there is not infrequently buphthalmus present on the side of the meningeal nævus In Lindau s disease ophthalmoscopic examination often shows the presence of the characteristic angiomata (v Hippel s disease) which have been shown to be of the same nature as the brain lesions In the Sturge Weber disease it should be noted that the degree extent and distri bution of the external vascular nævus vary greatly in different

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appearance and occasional slight urtication of the lesions on rubbing them suggested that the condition was really an extremely *telangiectatic variety of urticaria pigmentosa of adults* Dr W Freudenthal tells me that in a case of this telangiectatic type he has found tissue mast cells specially grouped about the minute blood vessels whereas in typical cases of urticaria pigmentosa the tissue mast cells constitute a more uniformly continuous layer in the cutis below the epidermis

(15) Here we may consider cases of recurrent non inflammatory erythema always recurring at the same sites *Frey s syndrome* is so called from Madame Lucie Frey who rediscovered (Kinnier Wilson) the condition in 1923 (*Rev Neurol* Paris 1923 **2** 97) This *auriculo temporal syndrome* consists of a localised reflex flushing and sweating at the side of the face on eating The cutaneous area affected is usually that of the auriculo temporal nerve and the condition is generally connected with scarring from wounds or suppuration in the parotid neighbourhood I described this syndrome which may be unilateral or bilateral long ago (*Trans Clin Soc Lond* 1897 1898 **31** 277 and *Med Press and Circ* 1905 **130** 261) My case was a bilateral one in a young man in whom appendicitis was followed by parotid buboes one on either side of the face both of which had to be opened Similar flushing and sweating best marked on taking acid or highly spiced food—general or limited to the head and neck—may occur as an idiosyncrasy in otherwise normal persons who have had no local injury of any kind Such reactions on eating undoubtedly represent a normal reflex in a greatly exaggerated form The limitation of the area of the reflex flushing and sweating in Frey s syndrome is certainly connected in some way with local nerve injury An excellent short article on the subject is that by A E Jones *St Barth Hosp Journ* 1942 war time series **3** 117

(16) *Relapsing febrile nodular non suppurative panniculitis* (*Weber Christian disease*) I originally described this very rare disease under the heading A case of relapsing non suppurative nodular panniculitis showing phagocytosis of subcutaneous fat cells by macrophages (*Brit Journ Derm* 1925 **37** 301) and Prof H A Christian in his very elaborate paper (*Arch Int Med* 1928 **42** 338) altered the name by the insertion of the word febrile The disease or syndrome is apparently similar to those described by Victor Pfeifer in 1892 and by Gilchrist and Ketron in 1916 but very little more has been discovered as to its ætiology (*see* R J Bailey *Journ Amer*

cases it is often not limited to the head, sometimes it is of *systematized distribution on one side* sometimes it involves both sides of the body, though to a different extent

A study of the whole subject of telangiectatic and angioma like dysplasias—and the probably invariable absence of any hereditary, or even familial, incidence—convinces me that the Sturge Weber disease must be due not to any genetic cause but to some accidental local injury (mechanical chemical or physical) to the ovum at some period after fertilization that is to say, to the embryo during early intra uterine life

(12) *Maffucci s syndrome* This is the eponymous name given by Carleton Elkington, Greenfield and Robb Smith (*Quart Journ Med* 1942 new series, 11 203) to a very rare association of dysplastic conditions namely, dyschondroplasia (Ollier s disease) and vascular hamartomata (cavernous angiomata and phlebectasia) The above authors can find no evidence to uphold the view that the whole syndrome is inherited Kast and v Recklinghausen published an elaborate study of a case (which has sometimes been supposed to be the earliest record) in *Virchow s Archiv* 1889 118 1

(13) *Telangiectases associated with purpuric lesions* This may occur as I have already stated when hypostatic toxic or inflammatory conditions cause hæmorrhagic lesions by local diapedesis, as well as local dilatations by yielding of vessel walls This combination is present in Majocchi s *purpura annularis telangiectodes* and in *purpuric pigmented lichenoid dermatitis* (Gougerot and Blum 1925) and often in *hypostatic dystrophic purpuric and pigmentary conditions* such as may be associated with varicose veins of the lower extremities notably if a toxic factor (for instance the use of drugs like abasin or adalin) be superadded

(14) *Telangiectasia macularis eruptiva perstans* an eruption of persistent red macules over the trunk and extremities especially in middle aged obese females Individual dilated blood vessels can usually not be distinguished by naked eye inspection I introduced the name in my original paper with Dr H Hellenschmied *Brit Journ Derm and Syph* 1930 42, 374 at the same time I pointed out that it was probably the same condition as *telangiectasies essentielles en plaques acquises* (Brocq) *See* H W Barber and Parkes Weber, *Internat Clinics*, 1932, series 42, 4 71 (with coloured illustrations) and Parkes Weber and H Rast *Acta Dermato Venereol* 1935 16 216 The patient is usually an obese middle aged woman beyond the climacteric period In the original paper I stated that the

Archer (*Lancet* 1927 2 595), both with organic disease of the central nervous system but without recurrent flushing and without obvious abdominal visceral disease Archer described his case as one of *multiple* cavernous angiomata of the sweat ducts

(19) In regard to punctate telangiectases or angiomata one ought to mention *angioma serpiginosum* (infective angioma nævus lupus) to which Sir Jonathan Hutchinson originally drew attention small reddish points spreading in lines and clusters and gradually in voluting with pigmentation In very slight cases the diagnosis may be difficult (cf F P Weber *Proc Roy Soc Med* Derm Section 1927 20 107) These cases are probably distinct from Schamberg s progressive pigmentary dermatosis (which occurs in males only) pigmented purpuric lichenoid dermatitis (Gougerot and Blum) and Majocchi s purpura (*see* above, group 13)

(20) Telangiectatic and pigmentary (hæmosiderotic) lesions are present in dystrophic *livedo racemosa* (*livedo reticularis*) as they also are in *erythema ab igne* (from constantly warming the legs at the fire) and *erythema a calore* (from repeated use of hot fomentations or electric pads) Telangiectases and pigmentary changes likewise occur in Jacobi s *poikiloderma atrophicans vasculare* (which may re semble lesions of X ray dermatitis) in *dermatomyositis* (as already mentioned) or *poikilodermatomyositis* in the familial *poikiloderma congenitale* of S Thomson (with which Tonseth s case of *cutis mar morata telangiectatica congenita* may be compared) in Bloch and Stauffer s *dyshormonal* poikiloderma like cases (1929) and in *Civatte s poikiloderma* of the face and neck in women also of course in the rare hereditary (Mendelian recessive) developmental disease *xeroderma pigmentosum* which has also been termed *angioma pig mentosum et atrophicum* and is characterised by extreme idiosyncratic over sensitivity of the skin towards sunlight

An important telangiectatic and pigmentary (hæmosiderotic) disease not yet mentioned is the so called *idiopathic multiple hæmor rhagic (first called pigmented) sarcoma of Kaposi* which is really appar ently a kind of pseudo sarcomatosis It is chiefly met with (at least as far as London is concerned) in middle aged or elderly Jewish males from Central Europe

In this group some types of *cutaneous sarcoid* and very unusual cases of *lupus erythematosus* should also be mentioned Patches of lupus erythematosus may show a telangiectatic appearance asso ciated with pigmentation the spots or macules of pigmentation having apparently been preceded by telangiectasis or telangiectatic

Med Assoc, 1937, 109, 1419) One of the causes may be the in gestion of iodides (or bromides?) in certain idiosyncratic individuals (F P Weber, *Brit Journ Derm* 1935, 47, 230) The subject is alluded to here only for comparison with other reddish swellings

(17) *Carcinoma telangiectaticum* Cases of carcinoma (of the breast), in which the carcinoma cells spread through the channels of the cutaneous blood capillaries which they dilate and partially block, so as to give rise to a curious red appearance of the skin of the thorax I suggested the above name (1933) in preference to the terms *erysipelas carcinomatosum* or *carcinoma erysipelatodes*, as I thought that the condition did not really resemble erysipelas at all (*cf* Parkes Weber *Intern Clinics*, 1935 series 45 3 145 with coloured plate) In this very rare condition the affected red or purple area, which may gradually extend almost completely round the thorax, is found on microscopic examination to contain numerous dilated blood capillaries more or less full of cancer cells The microscopic appearance differs altogether from those of cancer en cuirasse' and Paget s disease of the nipple—though all three conditions may be associated together

(18) *Miliary or punctiform telangiectasia or hæmangiomatosis with recurrent violent attacks of cutaneous flushing* I propose to call this *Steiner and Voerner s syndrome* from the case recorded by them in 1909 (*Deut Arch klin Med* 96 105) under the heading *Angiomatosis miliaris* These very rare cases seem occasionally to be connected with cancer of the liver (case in a man shown me by Dr Alice Carleton) or cancer somewhere in the abdominal or pelvic viscera In this connexion Sir Maurice A Cassidy s two cases of recurrent phenomenal flushing of the face (and to some extent of the trunk also) associated with carcinoma of abdominal viscera should be considered (*Proc Roy Soc Med* 1931 24 139 920 and 1934 27 220) The patients were both men aged 31 and 48 respectively In the coloured illustration of the younger man the flushed cheeks are covered with definite minute hair like telangiectases In both cases the necropsy showed metastatic growths in the liver in the younger case apparently secondary to primary prostatic carcinoma (which was accompanied by much diffuse pelvic fibrosis of inflam matory or malignant nature) in the older case secondary to primary carcinoma of the stomach (It is to the younger case that I would compare the man shown me by Dr Alice Carleton)

Cases of miliary hæmangiomatosis have been described by Wigley and Pether (*Proc Roy Soc Med* 1934 27 1574) and by B W C

VI

VARIETIES OF FLUSHING AND BLUSHING AND THE AURICULO-TEMPORAL AND ALLIED SYNDROMES[1]

Blushing and Flushing

THE phenomena of flushing and blushing are dependent on normal and abnormal conditions of the autonomic nervous system, and are intimately connected with normal and abnormal emotional sensitivity, and naturally with sex and age Amongst abnormal causative factors there is often excessive vasomotor erethism which may be familial and is sometimes associated with high blood pressure and hyperthyroidism Local and unilateral paroxysmal flushing may be accompanied by or compared to recurrent local or unilateral attacks of sweating waves of local or unilateral cutis anserina (*goose skin*) paroxysmal *salivation etc*

(1) Blushing which is by no means confined to the young has apparently become somewhat less in evidence during the present century probably owing to more natural education It is distinguished from other kinds of flushing by its emotional exciting causes viz shyness on being looked at (it can hardly occur in the dark or without the presence of other persons excepting from emotional thoughts or recollections) true or false modesty shame and sense of guiltiness fear of blushing (*ereuthophobia*) In spite of a possible hereditary predisposition to excessive blushing ordinary rational measures may be of use the doctor encouraging greater frankness and a wholesome objectivity in life discouraging (by explanation etc) too much self consciousness and the patient of course endeavouring to avoid secrets which he feels he ought to be ashamed of but facing up to them if they are there I need hardly mention the question of more elaborate (psycho analytical) methods of treatment for special cases In regard to the value of objectivity I would refer (as an analogy) to the occasional value of purposeful objective activity in preventing the onset of another common paroxysmal autonomic nervous attack namely sea sickness Doubtless many a boy in a rowing boat at a seaside holiday resort has found from personal experience that he can often avoid sea sickness by taking an energetic part in the actual rowing instead of sitting and doing nothing in a tossing boat

[1] After *Med Pre and Circ* 1944 **211** 199

erythema *Lupus erythematosus disseminatus* (so called) of chronic or subacute course may flare up with, or just before the commencement of, each menstrual period

(21) The *glomus tumour* of Masson (*arterial angiomyoneuroma glomangioma*) is a dysplastic benignant *organoid hamartoma*, arising from one of the neuromyo arterial peripheral vascular ('glomus') organs which were discovered by Masson during his research work in connexion with the origin of the glomus tumour These organs are normally present in the hands and feet, but have not been discovered elsewhere Consequently, a glomus tumour found on the thigh, shoulder or trunk may be termed heterotopic, and is rarer than one on a finger a characteristic site is in the nail bed beneath a nail A glomus tumour is cutaneous subcutaneous and forms a minute pinkish or bluish elevation which is extremely tender to pressure or knocks The resulting pain is apt to radiate widely and attacks may even occur spontaneously An unusually large ('giant') glomus tumour is likely to cause less rather than more pain than one of ordinary size Excision always removes the symptoms completely and no recurrence takes place The first case recognized clinically in London was described by W Freudenthal, R G Anderson and F Parkes Weber, with an elaborate histological study by Freudenthal in the *Brit Journ Dermatology* 1937, 49 151 163 The patient an otherwise healthy woman aged 50 years had had the minute nodule in the pad of the little finger of the left hand probably for 25 years and it had caused her much pain, excision removed the pain permanently

Glomus tumours are not likely to be confused with cutaneous or subcutaneous *leiomyomata* though the latter are sometimes tender to pressure and the skin over them may be reddish *Osler's nodes* (*Osler's sign*) in subacute bacterial endocarditis and in other septicæmic conditions (possibly complicated by so called mycotic aneurysms) are seen most typically on the fingers and hands but last too short a time to be confused with glomus tumours (*see* F Parkes Weber, *Quart Journ Med*, 1913 13 384) A strawberry like so called *granuloma telangiectaticum* (*granuloma pyogenicum*) on a finger is still less likely to be mistaken Small purplish superficial nodules occasionally appear over the abdomen or other parts in cases of *periarteritis nodosa* (compare A M Stewart *Proc Roy Soc Med* 1942, 35 18)

usually to be no special subjective excitement present Dermographism from rubbing by garments in uncovering the chest must be distinguished but may doubtless sometimes be an associated phenomenon (every case should be specially tested for urticaria factitia)

(4) Flushing of the face from anger and emotional excitement of various kinds is not rare especially in middle aged men of a plethoric type It may be compared to the swelling of a turkey s wattle with anger The story is told of a young man sitting as a naked model who on being angered by some important political news was observed not only to flush in his face and neck but to become bright red and lobster like over his whole body (H Campbell *op cit* p 53)

(5) The hectic flush of the face particularly in patients with late pulmonary tuberculosis should be mentioned here It may occur symmetrically on both sides of the face especially after taking food or may be better marked on one cheek, especially the side on which the patient lies Fortunately it is less commonly seen than it was formerly In this connexion I know of the case of a child who showed remarkable flushing on its chest after meals The child had a chronic empyema and after this was successfully treated surgically the flushing I believe ceased

(6) Rosaceous flushing of the face after eating drinking tea etc need not be discussed here In many cases fractional tests of the stomach contents reveal achlorhydria or hypochlorhydria or hyper chlorhydria and dietetic and general hygienic treatment may be of use Blotchy flushing of the face and upper part of the trunk after eating may occur in women who are also subject to true blushing of similar blotchy distribution

(7) Flushing and sweating best marked on taking acid or highly spiced food—limited to the head and neck or general—may occur as a remarkably uncomfortable peculiarity in otherwise normal persons who (unlike those in class 10) have had no suppurative lesion or surgical operation but it may apparently sometimes follow infectious diseases Such reactions on eating undoubtedly represent a normal reflex in a greatly exaggerated form Similar but *unilateral* cases of unknown origin may be mentioned as also unilateral cases of sweating only (In regard to unilateral and local predispositions compare Weber and Atkinson *Brit Journ Derm* 1928 40 454 and Weber *Med Press and Circ* 1928 176 377) As analogous to such cases the rare ones of unilateral cutis anserina (unilateral goose skin) may also be referred to

In some cases, as Darwin noted in his book on *The Expression of the Emotions* blushing is not confined to the face and neck but spreads in partly blotchy distribution over the shoulders and even sometimes over other parts of the body, especially if the abdomen is exposed (*cf* H Campbell, *Flushing and Morbid Blushing*, 1890, pp 52 53) An abnormal blotchy type of blushing may be inherited from a parent just as a tendency to too frequent ordinary blushing sometimes is (*cf* H Campbell *op cit* p 167)

Can blushing ever be voluntary? It cannot be denied that in male eyes of the last century blushing often heightened the charm of a beautiful maiden The same Greek word, ereuthos was applied to blushing as well as to the bloom and redness of fruit A lively girl may well have liked to add to her charms by a judicious blush The heart s action in certain individuals has apparently been affected either directly through the will or indirectly through voluntary emotional thought If vomiting cannot be induced directly by will power it may in certain individuals who vomit easily (that is to say those in whom the vomiting reflex is easily excited by relatively light stimuli) be voluntarily brought about indirectly by thinking of nauseating foods or tastes or smells or other nauseating subjects and ideas Probably the power of voluntary blushing is capable of being acquired in an analogous way, at least by certain (predisposed) individuals

(2) Climacteric and post climacteric flushing in women need merely be referred to here though there are many variations in degree and distribution and some cases may be associated with actual disease in the pelvic organs Emotional factors may likewise be present Dilatation of cutaneous vessels may sometimes occur in association with an attack of epilepsy or migraine[1] One of the numerous medical discoveries of quite modern times is the frequently successful treatment of menopausal disorders including excessive attacks of flushing by sexual hormones

(3) A blotchy type of flushing on the face neck and chest in post climacteric and elderly women is not rarely observed when the front of the thorax is uncovered for examination (*cf* F P Weber *Proc Roy Soc Med* 1935 28 731) It seems to occur especially in women with high blood pressure and tendency to hyperthyroidism and vasomotor erethism It resembles ordinary blushing in some respects but in spite of the emotional appearance there seems

[1] A disagreeable sensation of flushing and tension in the head may follow temporary faintness in elderly persons if on a strenuous walk they are suddenly stopped to examine something (dilatation of vessels following temporary angiospasm)

nected with some suppurative process in or surgical interference with the parotid gland—*see* above) Their patient was an otherwise healthy women, aged 22 who at the age of five years had had lymphatic glands excised from the right side of the neck A year after the operation on eating flushing occurred in the right sub mental region Two years later on eating profuse sweating over that same abnormal area made its appearance

The syndrome of crocodile tears to which they allude as analo gous is lacrimation occurring as a reflex response to eating it is always consequent to peripheral facial paralysis and has of course only been observed on the paralysed side In most authenticated cases the site of the lesion has been in the neighbourhood of the geniculate ganglion

Another analogous syndrome is abnormal inguinal sweating resulting from suppuration of an inguinal bubo

W C Wilson (*Clinical Science* London 1936 2 273) has studied four examples of sweating on the face during eating in relation to the question of innervation of the sweat glands of the face He concludes that the sweat glands of the human face have a double nerve supply sympathetic secretory fibres and an accessory set of fibres The sweating was proved to be the result of a reflex In one case the efferent impulses were conveyed by the sympathetic secre tory fibres in the other cases by the accessory fibres In relation to reflex sweating during eating the question of inhibitory nerve fibres to the sweat gland is discussed It is suggested by Wilson that exces sive reflex sweating during eating is related to a hyperactive condi tion of the sweat glands as indicated by their response to pilocarpine Such a hyperactive condition might follow degeneration of the sympathetic nerves

Some additional indirect light is thrown on the problem of localized hyperhidrosis by the study of cases of more or less com plete anhidrosis (absence of sweating) H R Richardson (*Journ Biol Chemistry* Baltimore 1926 67 397) made some careful observa tions in the case of a schoolboy who owing to a congenital ecto dermal defect had complete absence of sweat glands (confirmed by microscopical examination) His elimination of heat and water vapour was estimated It was found that with exercise the elimina tion of water did not increase as it does in normal individuals and his body temperature rose somewhat Exposure to external heat caused the body temperature to rise sharply and there was no increase in the quantity of water vaporized The author concluded that in

(8) Recurrent violent attacks of flushing of the face, and to some extent of the trunk also, associated with miliary telangiectasia or hæmangiomatosis In my paper on Some Telangiectatic and Other Anomalous Vascular Groups (*Med Press and Circ*, 1943, 210 219 224, group 18) I referred to such cases in men, associated with cancer in the abdomen and fibrotic adhesions in the pelvis I proposed the term Steiner and Voerner s syndrome, owing to the description by these two authors of a case in 1909 under the heading Angiomatosis miliaris, in which, however, there was no mention of cancer or abdominal or pelvic disease

(9) Here, I may also mention certain rare cases of chronic lupus erythematosus disseminatus in which a flare up occurs at the menstrual periods Permanently bright or dark red areas, such as for instance, certain cancerous conditions (e g the erythroplasia of Queyrat) and those which are occasionally met with in erythematous lichen planus and psoriasis, should have no place in the present paper

(10) The auriculo temporal and allied syndromes

The Auriculo-Temporal and Allied Syndromes

The so called auriculo temporal syndrome consists of a localized reflex flushing and sweating at the side of the face on eating The cutaneous area affected, in true cases, is that of the auriculo temporal nerve and the condition is connected with wounds or suppurative inflammation, which leave scarring in the parotid region When there has been a lesion on both sides the symptoms may be bilateral The case which I described long ago (*Trans Clin Soc Lond* 1897 1898 31, 277 and *Med Press and Circ* 1905 130 261) was a bilateral one in a young man in whom appendicitis was followed by parotid buboes one on either side of the face both of which had to be opened There is a good deal of scattered literature on the subject For an excellent short article *see* A E Jones *St Barth Hosp Journ* 1942 3, 117 The syndrome is sometimes called Frey s syndrome after Madame Lucie Frey who as Kinnier Wilson writes rediscovered the condition in 1933 (*Rev Neur* Paris 1923 11 97)

V Uprus J B Gaylor and E A Carmichael (*Brain* London 1934 57, 443) in their discussion on Localized Abnormal Flushing and Sweating on Eating give the account of a case differing from those of true auriculo temporal syndrome (which is always con

nected with some suppurative process in or surgical interference with the parotid gland—*see* above) Their patient was an otherwise healthy *woman* aged 22 who *at the age of five years had* had lymphatic glands excised from the right side of the neck A year after the operation on eating flushing occurred in the right sub mental region Two years later on eating profuse sweating over that same abnormal area made its appearance

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Some additional indirect light is thrown on the problem of localized hyperhidrosis by the study of cases of more or less complete anhidrosis (absence of sweating) H R Richardson (*Journ Biol Chemistry* Baltimore 1926 67 397) made some careful observations in the case of a schoolboy who owing to a congenital ectodermal defect had complete absence of sweat glands (confirmed by microscopical examination) His elimination of heat and water vapour was estimated It was found that with exercise the elimination of water did not increase as it does in normal individuals and his body temperature rose somewhat Exposure to external heat caused the body temperature to rise sharply and there was no increase in the quantity *of water vaporized The author concluded that* in

ordinary individuals the sweat glands constitute an emergency apparatus which is called upon only under exceptional conditions

To some extent Richardson's observations correspond with those of Mogens Fog (*Journ Amer Med Assoc*, 1936 106, 2040) A man aged 25 with nothing abnormal in his family history, at 21 years of age suffered from a long febrile disease (paratyphoid fever) After that he was unable to perspire (general acquired anhidrosis) under circumstances (heat fever work) which usually cause sweating, but instead of sweating he suffered from feelings of discomfort præcordial pain palpitation dyspnœa and congestive flushing of the skin particularly of the face The skin was dry and scaly, and microscopic examination (biopsy) showed that about one half of the sweat glands were present, while the other half had undergone degeneration

An observation by J M Berkman and B T Horton (*Proc Staff Meetings Mayo Clinic* 1937 12 168) suggests that absence of sweating may also be due to hysteria A woman, aged 36 complained of intolerance to heat since the age of 11 years, and had been supposed to be suffering from heat allergy In regard to the absence of sweating the patient behaved much as if she had undergone complete sympathectomy But an inability to walk at a normal rate and a psychological examination pointed to hysteria and it was frankly suggested to her that her whole trouble was the result of hysteria Then on being induced to remain in the sun her sweat apparatus commenced to act and she became literally drenched with perspiration

VII

'IDIOPATHIC' STRIÆ ATROPHICÆ OF PUBERTY IN A GIRL[1]

In ordinary cases striæ atrophicæ or striæ cutis distensæ can be explained as representing a method of cutaneous accommodation towards distension (physiological or pathological) when the skin is relatively insufficient—that is to say unable to adjust itself by its normal elastic distensibility In such cases a relatively too rapid growth or increase in bulk of the parts below the skin or a cause of chronic distension of some kind—such as a relatively excessive growth of subcutaneous fat muscle or bone (especially connected with puberty) mammary gland the pregnant uterus ascites tumours or subcutaneous œdema—leads to a splitting or cleavage in the deeper parts of the cutis manifested on the surface by the appearance of striæ atrophicæ which are at first generally red or purplish and in time usually become white and smaller as they heal up

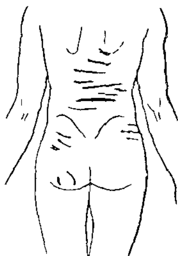
But here I wish to refer only to those cases of striæ not due to stretching of the skin that is to say the cases in which striæ have developed apparently in the absence of any special distension—in the absence of pregnancy ascites tumours subcutaneous œdema excessive subcutaneous fat and other usual causes In such cases the ordinary growth of the long bones muscles and subcutaneous fat seems to be associated with some insufficiency of the cutis (with perhaps deficiency of elasticity) which prevents the skin from adjusting itself to the parts beneath excepting by the process of multiple cleavage —that is to say by the formation of striæ atrophicæ Striæ of this mysterious kind occur occasionally in apparently healthy and in even athletic individuals about the period of puberty the skin failing to keep pace with the normally rapid growth of certain parts of the body such as the shoulders pelvis and thighs In 1932 I saw typical small striæ in the upper arms and upper parts of the thighs that developed without obvious cause in a muscular male student at an English university Striæ *in the absence of the ordinary causes* are however still better known to occur in connexion with enteric fever (notably the striæ patellares) and certain other infections although even in such cases the selective distribution of the striæ and whether they are symmetrical or more or less unilateral or not as I have elsewhere endeavoured to explain must be due partly to mechanical

[1] After *Lancet* 193 2 883 and 1347

causes, such as the position of the patient in bed, arrangement of pillows etc

Striæ form a prominent feature in the clinical syndrome attributed by Professor Harvey Cushing to pituitary basophilia or basophilic adenoma of the pituitary gland, and in 1932 I suggested that the relative insufficiency of the cutis which is a part factor in the causation of the cutaneous striæ in so called idiopathic and post infection cases may be due to a *temporary* basophilic hyperpituitarism associated with the period of rapid growth at and following puberty [3]

I have recently seen a remarkable example of *idiopathic striæ atrophicæ of puberty* in a rather thin tall girl aged 13¼ years She seems bodily and mentally developed two years or so beyond her age a good tennis player but somewhat lanky and over grown and inclined to slouch with bent back when sitting at her school work Her height is 167 cm and her weight is 51 5 kg She commenced to menstruate at 12 years of age and her mammæ and pubic hair are fairly developed She has a series of bright red transverse striæ (vergetures) over her back from the level of the tenth dorsal vertebra downwards (*see* figure) There are several older (white) striæ over the outer upper parts of both thighs and there are a few smaller red striæ over the left gluteal region It should be noted that her mother has had white striæ on the outer upper portions of both thighs since puberty though she feels sure that none of these striæ were ever red


Diagram showing position of the striæ on the patient's back and buttocks (a female aged 13¼ year)

In the case of the present girl the red transverse striæ over the

On this whole subject cf Weber F Parkes Unilateral Striæ Atrophicæ *Practitioner* 1917 99 453 also Weber Cutaneous Striæ *Brit Jour Derm and Syph* 1926 38 1 and 11 discussions *Proc Roy Soc Med* 1924 17 (Sect Derm p 45) and 1927 20 (Sect Dis Child p 11)

[3] Weber F Parkes *Urol and Cutan Rev* 193 36 ,31 The suggestion is not the same as that which I made in a short paper on the Causation of Striæ Atrophicæ Cutis (Vergetures) *Brit Med Journ* 19 8 1 2,5

back were first noticed by her mother about Christmas 1934 when they are said to have looked like very thin scratches at that time the patient had a slight attack of whooping cough In other respects she has enjoyed good health The causation of these idiopathic striæ atrophicæ of puberty is unknown unless my above suggestion on the subject is correct Anyhow the patient in question developed a tendency to the formation of such striæ at puberty as her mother did and probably her habitual stooping over her schoolwork has determined the position of the striæ—namely, on her back at right angles to the convexity of the bend It is possible that the infection with whooping cough played a part in the causation of the striæ (analogous to the better known part played by enteric fever in other cases) in association with the somewhat precocious onset of puberty The bright red stripes across her back were very annoying to the patient during summer at the seaside in regard to bathing

Postscript —In 1942 I heard that the above patient was in excellent general condition thin and active and doing useful work but the striæ on her back were still present (pink not white) not depressed nor raised above the general surface

SOMEWHAT SIMILAR STRIÆ IN A MALE[1]

In my article on idiopathic striæ atrophicæ of puberty in the *Lancet* of October 19 1935 I described a remarkable example of the condition in a healthy girl aged 13½ years The striæ which owing to their bright red colour must have been of fairly recent origin were transverse and somewhat irregularly situated over her back from the level of the tenth dorsal vertebra downwards That her rapid growth in height and general development had something to do with their onset there could be no doubt She seemed bodily and mentally developed at least two years beyond her age and had commenced to menstruate at 12 years of age The presumption was that the striæ would gradually become paler and less conspicuous and would give rise to no trouble unless from their appearance)



Diagram showing the position of the striæ on the patient's back (a man aged 44)

[1] *Lancet* 1935 2 1347

I have recently seen striæ atrophicæ of very similar distribution in a man, an English park labourer aged 44 (*see* figure) They are limited to the lower (lumbosacral) part of his back and are transversely, somewhat irregularly distributed more on the left than on the right side But they are quite pale, whereas those on the girl s back were red Obviously they are very old, the patient knew nothing about them and was apparently not even aware of their presence before his recent examination I can only think that they were connected in some way with rapid growth at puberty The patient himself came under observation for some totally different complaint but his history shows that he did indeed develop very rapidly at puberty for he was permitted to join the Army when he was only 15½ years old pretending that he was already 18 The two cases (in both of which the Wassermann reaction was negative) do really throw some light on each other and on the development, without any subjective symptoms of such cases of idiopathic striæ atrophicæ of puberty and also on the prognosis

Some would prefer to call the condition in both cases atrophodermia striata (linearis) by analogy with cases of atrophodermia (morphœa) guttata but I believe that the analogy is a false one though I have heard of a case in which idiopathic cutaneous striæ were combined with idiopathic drop like atrophy of the skin

VIII

SUBCUTANEOUS CALCINOSIS OR MULTIPLE CALCIFICATION IN THE SUBCUTANEOUS TISSUE[1]

The patient Anna G then aged 7 years, was admitted to the German Hospital on July 30 1912 on account of the presence of a large number of hard nodules in the subcutaneous tissue of the extremities and the portions of the trunk adjoining the extremities Most of the nodules were smaller than an average pea but some of them especially those on the buttocks and about the knees were much larger the larger nodules having apparently arisen by the coalescence of several smaller nodules The face head thorax and abdomen were practically free On the child s admission to the hospital the skin over one of the nodules was ulcerated and the skin was inflamed and adherent over one or two others but the nodules as a rule gave rise to no pain or tenderness and seemed to have developed without the child being aware of their existence The lymphatic glands in the groins and axillæ and some in the neck were moderately enlarged The liver and spleen could not be felt and the child seemed to be free from any visceral disease The urine contained no albumin or sugar There was no fever Brachial systolic blood pressure 110 mm Hg Ophthalmoscopic examination (right eye) showed nothing abnormal Blood examination (October 8 1912) Hæmoglobin 70 per cent red cells 4 070 000 per cubic millimetre of blood colour index 0 9 white cells (after a meal) 11 200 per cubic millimetre of blood The differential count of the white cells gave Polymorphonuclear neutrophiles 65 per cent small lymphocytes 27 per cent large lymphocytes 2 per cent large mononuclears 3 per cent transitionals 2 per cent eosinophils 1 per cent mast cells none in the count The red blood corpuscles appeared normal The coagulation time (estimated by Sir A E Wright s tubes at 25 C) was about three minutes On October 7 1912 Dr G R Ward kindly estimated the calcium index of the blood by W Blair Bell s method and found it to be 1 36 as against a normal average of about 0 9 It should be added that the child had some minute cutaneous punctiform telangiectases on the

[1] From Transactions of the XVIIth International Congress of Medicine London 1913 Section XIII Part 2 (August 8 1913) pp 179-188

[2] This case was shown and described at the Clinical Section of the Royal Society of Medicine on October 11 1912 (*Proceedings* 1913 6 14) *See also* F P Weber *British Journal of Children s Diseases* London 1913 10 97

outer surfaces of the upper eyelids, a few hair like telangiectases on both cheeks, and a tendency to mottling of the 'livedo reticulata kind on both forearms

According to the history obtained, the presence of hard sub cutaneous nodules was first noticed twelve months before the patient s admission to the hospital and since these were detected *many others had appeared One little nodule near the right knee* became very prominent and discharged spontaneously six weeks before admission In regard to the patient s past history, she was said to have been subject to skin eruptions, but the chief point was that in November 1909 she had been under treatment at a fever hospital for scarlet fever and that from that time to August 1910, she suffered successively from diphtheria paresis of the lower extremities (diphtheritic paralysis ?), a skin eruption somewhat resembling lichen ruber, pneumonia an abscess in the right axilla and an abscess at the back of the neck a corneal ulcer (marantic ?) of the left eye and left sided otorrhœa The corneal ulcer perforated (giving rise to considerable prolapse of the iris) but ultimately healed up again During the latter period of this succession of illnesses the patient was in the German Hospital She left the hospital on August 1 1910 but was readmitted in September of the same year for temporary fever of uncertain origin Since that time the child s condition seemed to have remained satisfactory until the appearance of the subcutaneous nodules first attracted the parents attention about August 1911 In regard to the family history there *was little to be said The father a traveller was a healthy looking* man who had never suffered from any venereal disease The mother aged 35 subject to epilepsy had had no miscarriages or abortions Of the patient s four brothers and one sister one brother had had rheumatic fever and another had had tuberculous disease of the left ankle joint (the others said to be healthy)

That the subcutaneous nodules in the present case consisted largely of calcareous material was proved both by Rontgen ray examination and by chemical analysis The skiagrams (taken by Dr G Dorner in August 1912) showed how numerous these calcareous infiltrations were (there must have been over a hundred of them in the patient s limbs) and suggested likewise that the larger nodules were formed by the coalescence of smaller foci The nodules occasionally became inflamed and softened the skin over them tended to become ad herent and if they were then left to themselves thin purulent matter mixed with calcareous debris would doubtless be gradually

extruded through a fistulous opening in the skin Two such softened nodules had been excised and examined The gritty material was found to consist of calcium carbonate and calcium phosphate (The addition of weak sulphuric acid under the microscope was followed by the separation of bubbles of carbonic acid gas and by the formation of acicular crystals of calcium sulphate the ammonium molybdate test showed the presence of phosphates) No tubercle bacilli or other microbes were detected in the contents of the nodules Culture tubes of glycerine agar glucose agar and egg agar were inoculated but remained sterile Another concretion was examined for uric acid by the murexide test but with negative result Microscopical sections of a softening nodule showed that the nodules consisted of a sponge like matrix of subcutaneous connective tissue in the interstices of which the granular particles of lime salts were embedded Thus a microscopical section stained with hæmatoxylin shows many structureless islands (necrotic debris) from which the lime salts have been removed (by the weak hydrochloric acid ordinarily used for decalcifying) embedded in a spongy framework of connective tissue which is undergoing inflammatory small cell infiltration (inflammatory softening) previous to the process of breaking down and discharging The nodule in fact consists of granules of calcareous material held together by a fibrous frame work and there is nothing of the complete (stone like) calcification met with in calcified tuberculous (caseous) foci and in calcified gummata The diffuseness of the process of calcification explains why in this kind of calcification the concretions cannot be shelled out when an attempt is made to remove them

Further skiagrams (kindly taken by Dr Finzi) of the abdomen thorax and axillæ gave no evidence of calcification in the axillary intrathoracic or intra abdominal lymphatic glands or in any of the thoracic or abdominal viscera

Since July 1912 the patient has been continuously under observation She has had an ordinary diet and has had a good appetite Her general health has remained excellent though she has had some otorrhœa from her old ear disease The nodules of calcification have certainly decreased especially those about the hips and buttocks This is well shown by skiagrams taken on July 31 1913 by Dr R W A Salmond to compare with those taken a year ago by Dr Dorner Probably this is the first case of the kind showing such marked regression of the lesions Dr Salmond reports Compared with the original X ray plates the patches of calcification show a

marked decrease This is more especially seen in the upper part of the thighs and hips The subcutaneous nodules about the knees are still very conspicuous They form at present the most striking feature of the case The lymphatic glands of the axillæ and groins, and some in the neck are still slightly enlarged

During most of the last year the child has been taking syrup of iodide of iron, and during a great portion of the time small doses of potassium iodide as well All medicine was temporarily discontinued on December 23 of last year and on January 12 Dr G R Ward found the calcium index of the blood only 0 855 He estimated it again on July 31 after the patient had for some time been having rather large doses of iodide of iron it was then very high namely 1 46 It is worth while mentioning that on that occasion he likewise estimated the resistance of the patient s red blood cells to graduated hypotonic saline solutions and found that hæmolysis occurred with between 0 3 and 0 35 per cent sodium chloride solutions

In regard to the ætiology of the calcareous nodules syphilis and tuberculosis may be practically excluded by reason of the various above mentioned data Moreover both Wassermann s reaction for syphilis (tried at the Lister Institute) and von Pirquet s cuti reaction for tuberculosis gave a negative result the complete absence of fever is likewise an important point The case is not at all like one of myositis ossificans for the muscles (at all events as yet) seem not to be affected there is no abnormal formation of true bone and the inflammatory softening of the calcareous nodules is different to anything which occurs in myositis ossificans Moreover the child has no shortness (microdactyly) of the great toes such as has been recorded in several cases of myositis ossificans The scattered literature of the subject shows however that the child s condition can be regarded as one of a definite disease as distinct at least as myositis ossificans and many other diseases

Calcinosis is probably the most convenient term to be used for the disease in question and more advanced cases have been described under the headings Calcinosis interstitialis and Calcinosis universalis [17] Possibly the chief danger is the risk of septic infection associated with the breaking down and discharge of the calcareous nodules but in the present case (Anna G) there has been no breaking down of this kind for quite a long while

There is a condition occurring in rather older subjects which possibly represents a more chronic and less severe variety of the

same disease [10 14 15 18] In that condition the calcareous deposits occur chiefly in the subcutaneous cushions of the finger tips and at the elbows, about the olecranon, and sometimes in the toes Such cases have been recently demonstrated in England by Scholefield and Weber [13] by Haldin Davis,[3] and by W K Hunter[6] the patients are all subject to Raynaud s phenomena and most of them gradually develop a sclerodermatous change chiefly in the fingers (sclero dactylia) Sir William Osler has met with two such cases of scleroderma associated with subcutaneous calcification

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IMPROVEMENT OCCURRING IN CASES OF CALCINOSIS UNIVERSALIS IN CHILDREN[1]

In the September part of the *British Journal of Dermatology and Syphilis* (1935 47 340 52) Dr Mason Bolam described and discussed a very interesting case of the metabolic or universal type of calcinosis in a little girl aged 6 years But neither he nor most other recent writers seem to be acquainted with the striking improvement which has been observed in certain cases of similar type The first case showing such improvement was demonstrated and described by me at the Seventeenth International Congress of Medicine (Section of Dermatology and Syphilis) which was held in London in August 1913 This case was also the first case of the universal or generalized (metabolic) type of calcinosis demonstrated or described in the English language and one amongst the first cases of calcinosis without sclerodermia recorded anywhere

Though at the Congress it excited the interest of Professor Unna of Hamburg Professor Riehl of Vienna Professor Dind of Lausanne and other dermatologists present my case has almost completely been overlooked in subsequent references to the literature of the subject I am therefore justified I think in giving a short *resume* of the case here

The patient Anna G then aged 7 years was admitted to the German Hospital on July 30 1912[2] on account of the presence of a large number of hard nodules in the subcutaneous tissue of the extremities and the portions of the trunk adjoining the extremities Most of the nodules were smaller than an average pea but some of them especially those on the buttocks and about the knees were much larger the larger nodules having apparently arisen by the coalescence of several smaller nodules The face head thorax and abdomen were practically free On the child s admission to the hospital the skin over one of the nodules was ulcerated and the skin was inflamed and adherent over one or two others but the nodules as a rule gave rise to no pain or tenderness and seemed to have developed without the child being aware of their existence

[1] From *B it J u D mat* 1935 47 400

[2] F Park s Weber Subcutaneous Calcino *P de f th Se nt enth I te n tional Co f M dicin* Section XIII Pa t 2 (meet ng of Augu t 8 1913) pp 179-88

I h ca as al o 3 ov n and described at the Cl nical Sect on of the Royal Society of M d in on October 11 1912 (*P oc ed ng* 1913 6 14) *S al* F I Weber *B t J u n Ch ld D* London 1913 10 97

The lymphatic glands in the groins and axillæ, and some in the neck, were moderately enlarged The liver and spleen could not be felt and the child seemed to be free from any visceral disease

It should be added that the child had some minute cutaneous punctiform telangiectases on the outer surfaces of the upper eyelids a few hair like telangiectases on both cheeks and a tendency to mottling of the livedo reticulata kind on both forearms

I will not repeat all that is stated in the previous section Suffice it to say that nodules of calcification certainly *markedly* decreased, especially *those about the hips and buttocks This was well shown* by skiagrams taken on July 31 1913, to compare with those taken a year previously

In the account of my case at the International Medical Congress (August, 1913) I referred to Max Verse s excellent paper on Calcinosis Universalis (Ziegler s *Beitrage* 1912 53 212) which included an analysis of previous literature on the whole subject

Unfortunately the patient left England with her parents some time afterwards and was lost sight of but in 1932 R L J Kennedy[4] described the case of a girl with calcinosis and scleroderma in which the calcareous deposits partially disappeared during treatment by a ketogenic diet That patient was aged 6 years when seen in September 1928 and in June 1932 a very remarkable improvement could be demonstrated Dr Kennedy, in the literature of the subject had been unable to find any record of a similar clearing up of extensive calcareous deposits

In 1931 J Craig and A Lyall[5] had described the case of a girl aged 5¼ years with calcinosis universalis (without any scleroderma), in which improvement followed the administration of di sodium phosphate by the mouth In a few weeks time the calcareous deposits were shown by X ray examination to have greatly diminished Treatment by syrup of the iodide of iron had previously been tried without appreciable benefit

It is therefore quite certain that in a few cases of calcinosis in children great diminution of the calcareous deposits as judged

[4] R L J Kennedy *Collected Papers of the Mayo Clinic* 1933 (for the year 193) 24 1087-9

[5] J Craig and A Lyall A Case of Calcinosis Universalis and a Suggested Method of Treatment *Brit Journ Child Dis* 1931 28 9 34

especially by careful X ray examination has been observed under various methods of treatment It may be noted that all the three cases above referred to were in girls It is possible that calcinosis universalis is less rare in females than in males

Postscript (1946) —For a review of the whole literature on Cutaneous and Subcutaneous Calcinosis *see* F R B Atkinson and F Parkes Weber *Brit Journ Dermatology* 1938 **50** 267

X

MACROGENITOSOMIA OF THE 'JUVENILE HERCULES TYPE' WITH A SWELLING IN THE SUPERIOR MEDIASTINUM

(A New Syndrome ?)[1]

MACROGENITOSOMIA that is to say, strikingly precocious sexual and bodily growth is of relatively rare occurrence and when it occurs, is seldom the only obviously abnormal finding There may be some thing peculiar not only in the degree but also in the character of the excessive sexual development for instance there may be marked heterosexual features especially so called virilism in females When in children there is hyperplasia or a primary tumour of an endocrine gland it is natural to suppose that this either directly by the hor mones which it produces or indirectly by upsetting the endocrine balance is the cause of the macrogenitosomia and other associated sexual abnormalities

In their paper of May 10 1906, Guthrie and Emery (*Trans Clin Soc Lond*, 1907 **40** 175) wrote We desire to support Parkes Weber s contention that two distinct types of cases are seen in connexion with hypernephromata (they mean of course, cortical hypernephromata) namely (1) The precociously obese type (2) the muscular or *infant Hercules* type The precociously obese type may be seen in either sex, the muscular type seems to be chiefly met with in males By *precocious obesity* a term first used by Parkes Weber we think of the obesity commonly seen in middle aged men and women and not merely plumpness or excessive adiposity such as may be produced in infancy and childhood by excess of patent foods In precocious obesity the features are bloated the cheeks swell with fatness the complexion is dusky and congested

From this second type it is now clear that the clinical symptoms of Cushing s disease due as Cushing thought to a functioning basophil adenoma of the anterior lobe of the pituitary gland cannot always be distinguished In 1935 A C Crooke (*Journ Path and Bact* **41**, 339) described a remarkable hyaline change in the basophil cells of the pituitary gland which he found in all cases exhibiting Cush ing s syndrome whether or not an actual basophil adenoma was detected And it must be noted that Crooke s hyaline change and

[1]After my paper with Dr M Wohl *Med Press and Circ* 1944 **211** 2 (with Dr Wohl s kind permission)

the presence of minute basophil adenomata may, perhaps simply be the result (and evidence) of excessive functional activity of the pituitary basophil cells—which excessive activity may be secondary to some primary disturbance of other endocrine organs notably the suprarenal cortex Crooke also found his hyaline change in the pituitary gland in the cases of primary malignant neoplasm of the thymus with endocrine symptoms somewhat resembling Cushing s syndrome which had been described in 1931 by Leyton Turnbull and Bratton (*Journ Path and Bact* 34 635) To these cases of the Leyton Turnbull Bratton syndrome we shall refer again further on

A muscular type of precocious development has been found con nected with certain primary testicular tumours for a short summary on macrogenitosomia with tumours of the testes and ovaries *see* that by F Parkes Weber included in a paper by R P Rowland and G W Nicholson in 1929 (*Guy s Hospital Reports* 79 405)

Some of the most interesting cases of macrogenitosomia—mostly in boys of the muscular type—are those associated with tumours of the pineal body or the mid brain and hypothalamus The subject has been discussed among others by Le Marquand and D S Russell (Royal Berkshire Hospital Reports 1934 1935 p 31) in whose case a boy aged 4 years and 10 months at his death a small tumour was found occupying the interpeduncular space attached to the right corpus mammilare and the tuber cinereum The tumour appeared to be a redundant portion of the brain tissue formed by a developmental error—a hamartoma or choristoma of Albrecht It was therefore quite unrelated to an endocrine tumour of any kind There was no internal hydrocephalus in that case to produce pres sure and complicate the question of causation of the macrogenito somia A comparable case of macrogenitosomia is that described by H Cohen J Pennybacker and D S Russell at the annual meeting of the Association of Physicians of Great Britain and Ireland on June 12 1943 (*Quart Journ Med* 1943 12 262) A boy of seven years had the genital and skeletal development of a youth of 15 years but showed no intellectual precocity There was a cystic astrocytoma involving the third ventricle the right temporal lobe and the hypothalamus including the mammillary bodies and causing hydrocephalus and (amongst other clinical signs) papillœdema The pineal body was normal and Professor Cohen said he doubted if any incretory function could ever be assigned to that body

There has been much experimentation observation and dis

cussion regarding the probable functions of the normal thymus gland, and whether or not one is justified in regarding it as an endocrine organ The balance of opinion has gradually become more and more in favour of the thymus acting as an endocrine organ even (in many individuals) during adult life G Worms and H P Klotz (*Le Thymus* Paris, 1935 94) sum up the results of observations by many workers on the subject regarding the interaction of the thymus and generative organs The development of the generative organs is directly dependent on good functioning of the thymus their evolution at puberty provokes the involution of the thymus and this thymic involution can be retarded or even prevented by castration A Crotti (*Diseases of the Thyroid, Parathyroid and Thymus* London 1938, p 1028) writes that it has been shown by Gudernatsch (1914) and Rowntree and others (1935) that rats born from parents and ancestors who have been hyperthymized for generations show enormous somatic development sexual precocity, and seem to possess a keen intelligence

Many pathological observations suggest that the thymus can exert an important influence of some kind even in adult life How else can one explain the good effect of thymectomy in many cases of myasthenia gravis (for a short summary on this subject *see* F Parkes Weber and K Blum Lympho epithelioma of the Thymus *Journ Neur and Psychopathol* 1942 5 148 *see* also recent summary by M Nellen *Brit Med Journ* 1943 2 778) Then there are the above mentioned cases of a primary malignant tumour (described as medullary small celled carcinoma) of the thymus with hypertrophy of suprarenal cortex and thyroid gland and symptoms somewhat resembling those of Cushing s syndrome (Leyton Turnbull and Bratton s paper on this subject has already been referred to) E J Kepler and others in a communication on Polyglandular Dyscrasias involving Abnormalities of Sexual Characteristics *Proc Staff Meeting Mayo Clinic* 1933 8 102 (Case 4) described the case of a woman aged 46 years with symptoms somewhat resembling those of Cushing s syndrome The post mortem examination showed a thymus tumour and nothing abnormal was found in the pituitary gland till *Crooke later demonstrated the presence of his* pituitary basophilic cell hyaline change (*see* above) The case could be regarded as an adult example of the Leyton Turnbull Bratton syndrome In this connexion also Leyton *et al* in their paper (*loc cit*) refer to the case of a woman aged 64 years (described by J B Duguid and A M Kennedy *Journ Path and Bact*, 1930, 33, 93) as

one in some respects to be compared with their cases She had glycosuria, enlargement of the suprarenal bodies and colloid goitre together with a small celled medullary carcinoma of the thymus Furthermore, as to some extent bearing on the subject, Mr J E H Roberts has kindly permitted us to mention that at the meeting of the Royal Society of Medicine (Clinical Section) on December 10 1943 he showed a boy aged 16 years with abnormally small testes and bilateral gynæcomastia (*Proc Roy Soc Med*, 1943 1944 37 157) The boy had been treated by deep X rays for what was probably a large rapidly growing (malignant) primary thymic tumour mainly in the anterior mediastinum and causing alarming pressure signs As a result of the treatment the tumour had dis appeared Skiagraphic examination after six months showed no recurrence The smallness of the testes remained unaltered The enlargement of the breasts which had come on at the time when the thoracic pressure signs commenced (suggesting causal connexion with the tumour) somewhat diminished with the disappearance of the tumour, so Mr Roberts and the patient himself, thought

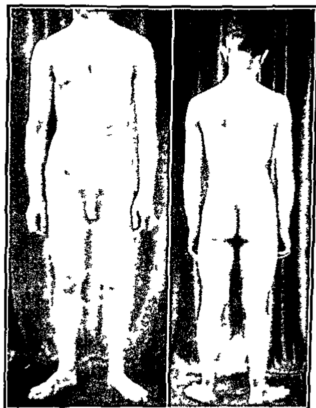
We will now clinically describe the case of a boy aged 14½ years with macrogenitosomia of what we would term the juvenile Hercules type who has a swelling in the superior mediastinum probably an enlarged thymus or a thymic neoplasm

Description of Case

The patient D C aged 14½ years when first examined by us at the commencement of October, 1943 is a dark complexioned boy born in London on February 20 1929 of Russian Jewish parents He is 5 ft 7½ in (=1 71 metres) in height and 9 st 12 lb (63 3 kilograms) in weight and has the muscular and external sexual development of a muscular sexually fully developed adult man There is no excess of subcutaneous fat and the perfectly symmetrical muscular contour of his body and limbs especially his lower limbs would rival that of the statue of a well built Greek athlete or young Hercules There is a good deal of hair over his sternum and lower limbs in addition to his facial and pubic hair which latter is abundant and of male distribution (*see* photographs figs 1 and 2) A congenital developmental defect which should be mentioned here is an extensive systematized pigmentary *nævus unius lateris* of the left half of his trunk and left upper limb His intelli gence is slightly above the normal average for his age In his general manner and behaviour he gives one a somewhat languid and rather

shy impression On the sexual side he seems like a normal young adult He has occasional erections in connexion with sexual thoughts or sights though *no seminal emissions*

History —According to his mother he had rheumatic fever some years ago and was sent, on account of a 'weak heart, to a special school and while there he was not allowed to play football and other games Since then he has played football, but, according to



Figs 1 and — Photograph October o 1943
(*See account in t t*)

his mother, this does not suit him He has always tended to get too easily out of breath and for some time has not rarely had a pain in the lower left region of the thorax occasionally also across the upper part of his chest As to his macrogenitosomia his great increase in general bodily development, according to his mother and the patient himself commenced three years ago (previously he was like other

boys) It seems that the precocious sexual development com menced about the same time During the last nine months he has had to shave his face There seems to be nothing special in the family history, excepting that a first cousin of the patient, a woman aged about 50 years has apparently had deep X ray treatment for an internal growth of some kind



Fig 3 —Skiagram of thorax October 25 1943
(*See account in text*)

Clinical Examination and Present Findings —By ordinary examination we find no definite sign of disease in thorax or abdomen No enlargement of liver spleen or superficial lymphatic glands The thyroid

gland does not seem to be abnormal Knee jerks equal moderately active Dr C Markus kindly examined the patient's eyes in particular with regard to the fundi pupils and muscles and found nothing abnormal, the visual fields were free for hand movements Blood count (October 20 1943) hæmoglobin 88 per cent erythrocytes 4,680 000 colour index = 0 94, leucocytes 6 100 (polys 53 per cent lymphos 39 per cent monos 8 per cent) Urine specific gravity 1012 to 1020, acid, clear medium yellow colour, nothing abnormal detected by ordinary or microscopical examination Blood sugar and sugar tolerance curve normal Blood cholesterol 180 mg per cent Blood serum calcium 9 8 mg per cent Blood Wassermann reaction negative Blood sedimentation no acceleration Brachial blood pressure 110/66 mm Hg Pulse 66 regular Electrocardiogram (Dr F P Duras) nothing abnormal except that the S—T segment is slightly depressed in lead three Fractional tests of stomach contents after a test meal could unfortunately not be carried out

X ray Examination (Dr F G Wood) —A lobular tumour is visible in the superior mediastinum in close relation to the aorta (*see* illustration fig 3) It shows transmitted pulsation (to the left) on kymography A tomograph section at 8 cm shows it extending downwards some distance below the bifurcation of the trachea A barium swallow shows nothing abnormal—no compression of the œsophagus Examination of the stomach and intestines by a barium meal shows nothing abnormal The exact position and outline of the kidneys cannot be made out (an examination by uroselektan or uropac was for certain reasons not carried out though it might have demonstrated the position of the renal pelves and ureters in regard to possible presence of suprarenal cortical hyperplasia or tumour) Radiograms of both hands and wrists show full adult ossification excepting that the distal epiphyses of radius and ulna are not quite joined yet By skiagraphic examination Dr Wood can find nothing abnormal in regard to the pituitary fossa and skull

Dentition —All the second teeth are in full evidence except the four wisdom teeth Dr Wood says that the lower molars have an extra (fifth) cusp on the lingual aspect

Mr F Lloyd Warren of the Chester Beatty Research Institute Royal Cancer Hospital kindly undertook to estimate the excretion of 17 ketosteroid in the patient s urine He reported that the assay came out at 14 3 mgm of 17 ketosteroid per day which he regarded as an average normal figure for an adult male

MEASUREMENTS CAREFULLY TAKEN ON DECEMBER 31, 1943

Compared to normal averages for boy of 15 years

(After Le Marquand and Tozer)

		Normal average
Circumference of the head above the eyebrows	23 in	21 8 in
Circumference of the chest at nipple level	33 5 in	30 3 in
Circumference of the abdomen at umbilical level	28 5 in	26 4 in
Span with outstretched arms from tip of one middle finger to tip of the other	70 5 in	61 7 to 65 5 in
Height	67 5 in	60 3 to 64 5 in
Lower measurement (from the top of the pubic bone to the sole of the foot)	33 5 in	30 2 to 33 2 in
Upper measurement (from the top of the pubic bone to the top of the head)	34 in	29 3 to 32 3 in
Weight	139 lb	89 4 to 113 4 lb

We have specially to thank Dr H M Turnbull Mr F Lloyd Warren Dr F G Wood Dr C Markus and Dr F P Duras for their help in the examination of this case

Remarks

How are we to explain this case? The mass in the upper mediastinum is almost certainly either a large (?persistent and hypertrophied) thymus or a primary tumour of the thymus If it is a persistent hypertrophied thymus it is a developmental abnormality An individual with a developmental abnormality of one kind has not rarely also one or more developmental abnormalities of other kinds This boy has also the systematized *nævus unius lateris*—which is a developmental abnormality—and a still more pronounced developmental (late developmental) abnormality, namely the precocious sexual and general development or macrogenitosomia Some might therefore regard the case merely as one of multiple developmental abnormalities—aberrations in growth associated but not causally connected with each other

On the other hand, *we believe* that the thymus must be regarded as an endocrine organ (compare our references to the subject in the preliminary portion of this paper), and that in our patient this endocrine organ is enlarged by hypertrophy or hyperplasia or functioning neoplasm (endocrine tumour) of its endocrine constituents If that is really so, the macrogenitosomia must be regarded as a manifestation of response towards excess of thymus hormones the active endocrine constituents of the thymus having become greatly increased instead of undergoing an atrophic process, as they should do at normal puberty The results of what one may call artificial experimental hyperthymism of rats (Rowntree and others) to which we have already referred, certainly seem to support this view

Macrogenitosomia of thymic origin may be a feature of the Leyton Turnbull Bratton syndrome if it occurs in young subjects (*see above*) *but this is of a different type to the macrogenitosomia in our* case which is a definite example of the muscular or juvenile Hercules type Just as endocrine tumours of the suprarenal cortex in children may cause macrogenitosomia either of the precocious *obesity type (resembling some of the main features of Cushing's* syndrome) or of the muscular or infant Hercules type—probably according to the sex and bodily soil on which the suprarenal cortical hormones act—may not endocrine tumours or functioning hyper*plasia of the thymus in children cause macrogenitosomia either of* the precocious obesity type somewhat resembling Cushing's syndrome (as in the Leyton Turnbull Bratton syndrome) or of the muscular or juvenile Hercules type as in our present case? This *case would then be a new syndrome (perhaps the first published* example) namely thymic macrogenitosomia of the infant (juvenile) Hercules type—constituting a kind of missing link in the chain of recorded types As in suprarenal cortical endocrine tumours the *infant Hercules type of macrogenitosomia occurs only in some cases,* those in which the bodily soil must be supposed to be favourable and only in males so in endocrine tumours or functioning hyperplasia of the thymus the infant (juvenile) Hercules type of macro*genitosomia will probably be found to occur only in males and only* in certain males, doubtless those whose bodily soil is in some way favourable for the development of that type of macrogenitosomia

In regard to treatment of the case we intend to recommend deep X ray treatment that is to say if there is any *evidence that the* tumour is increasing

If our explanation (as above given) of the present case be regarded as probably correct it may well be asked how we would account for the strikingly different syndrome in the case to which Mr J E H Roberts has kindly allowed us to refer In that case there was apparently a rapidly growing malignant but extremely radio sensitive primary tumour of the thymus whereas in our case the presumably primary thymic tumour or functioning thymic hyper plasia seems to be (as yet) smaller and less active We would suggest however that this difference in results may be due less to differ ence in the thymic hormones at work than to difference in the bodily soil on which the hormones have been acting Both patients are males but ours is younger than Mr Roberts and his body may therefore have been more susceptible to the action of any hormones which promote sexual and bodily growth Moreover it is quite possible that in our case there was already a specially virile tendency towards early sexual and bodily development whereas in Mr Roberts case there may have been low virility (note the smallness of the testes) and the sexual balance may have been more easily upset towards the female side (note the gynæcomastia) by shock action of the rapidly growing endocrine thymic tumour There may likewise have been some original potential difference between the two cases in regard to the reactive power of the suprarenal cortex and other endocrine organs secondarily involved by the upset of the normal endocrine balance

Postscript by Dr Parkes Weber December 1945 —The patient D C has developed into a practically normal individual allowing for the tendency to somewhat premature development in dark com plexioned Russian Jewish children He is of the lean muscular type and very hairy especially of course in the pubic region but his penis and testicles are not particularly large Nothing definitely abnormal is now seen by skiagraphic examination of the thorax The macrogenitosomia apparently represented a developmental phase connected with delayed involution of a rather large thymus No X ray treatment has been employed The temporary develop mental syndrome in this case may probably be regarded as a non malignant analogue of the *Leyton Turnbull Bratton thymus syndrome* the delayed involution of a large thymus being the main causative factor Curiously enough I know of no published account of a similar case although it is unlikely that such cases are in reality extremely rare

XI

GYNÆCOMASTIA, ESPECIALLY IN REGARD TO THE EFFECTS OF ENDOCRINE TUMOURS[1]

It is now almost a platitude to say that in regard to the causation of somatic sexual peculiarities not only the effect of—or the reaction towards—hormones has to be considered but also the zygotic make up of the individual, including hereditary tendencies temporarily modified by age and other circumstances which help to constitute the soil on which the hormones work

In regard to so called sexual characters —including both somatic and psychical ones—no individual is completely and only male or female The hermaphrodite (androgynoid and gynandroid) features may vary in degree, kind and situation from slight hetero sexual abnormality in secondary sexual characters (almost within normal limits) such as in the distribution of the pubic hair, to true (so called glandular) hermaphroditism and to psychical bisexuality and homosexuality

It is quite obvious that the zygotic make up of the body may be such that one side of the body is more predisposed to react towards hormonic influence than the other and that one region or organ may be the only one to react In regard to such potential unilaterality and local predispositions *see* Weber and Atkinson *Brit Journ Derm* *1928* *40*, *454* and F P Weber *Med Press and Circ* 1928 **176** 327

A curious case to which one may refer in this connexion is that of a man aged 59 years who had apparently always had a hetero topic mammary rudiment on the inner side of the right thigh This had in recent years without any obvious cause developed into a regular gynæcomastia of the size of a female breast (H Hirschfield *Med Klinik* 1933 **29** 1309)

In regard to the importance of the age factor in the production of hormonic effects, I will mention the well known occasional occurrence of temporary gynæcomastia in boys at puberty which seems to be due to a temporary burst of endocrine activity in the testes and possibly in the adrenal cortex the endocrine secretions of these organs probably contain not only androgen elements but also œstrogen elements sufficient to produce temporary mammary hyper trophy in boys who happen to be predisposed by their zygotic make up—that is to say by a potential local feminism manifesting itself at that particular period of life For an instance *see* F P Weber *Med*

[1]From *Med Press and Circ* 1944 **211** 155

Press and Circ 1928, 177 425 I mention this merely to emphasize the age factor in the production of hormonic effects I suppose however, that any cause which diminishes the androgen side of the sexual hormonic balance may in predisposed individuals indirectly give rise to gynæcomastia It may perhaps be compared to the temporary gynæcomastia sometimes produced by stilbœstrol treatment and temporary gynæcomastia after giving doca i e desoxy corticosterone acetate (R D Lawrence, *Brit Med Journ*, 1943 1 12) Perhaps the gynæcomastia said to have been noted with hepatic cirrhosis in a few cases may be explained in this way

In this paper I shall limit myself to the question of gynæcomastia in relation to endocrine tumours and by the term endocrine tumour I mean one made up of neoplastic cells which have arisen from the functioning endocrine cells of an endocrine organ and which continue to possess more or less of their original functional activity in spite of having become neoplastic (cf F P Weber *Proc Roy Soc Med* 1929 22 415 *Brit Med Journ* 1929 2 533 *Endocrine Tumours and other Essays* London 1936 pp 11 50)

From the preceding paragraphs it is I think quite clear that my remarks will apply to unilateral as well as to bilateral gynæcomastia that is to say to a morphological feminism in one or both breasts whether or not associated with features of morphological feminism in other parts of the body

Gynæcomastia and Endocrine Tumours of the Adrenal Cortex

Everything seemed to show that an effect of cortical hypernephromata was to induce features of virilism in females and to increase virilistic features in males but in a paper of 1926 (F P Weber *Brit Journ Derm* 1926 38 7 8) Dr J P zum Busch kindly allowed me to describe a case which he had shown me in 1915 with what one might call acute mammary feminism resulting as a hormonic effect from a rapidly growing primary malignant hypernephroma of the left suprarenal cortex In that case the hormone from the endocrine tumour had apparently stimulated the male mamma to take on an active secreting function normal to the female mamma The remarkable Bittorf Mathias case (E Mathias *Virchows Arch* 192_ 236 446) in a man aged 26 years was quite analogous (cf also F P Weber *Lancet* 1926 1, 1034)

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[1]From *Med Press and Circ* 1944 **211** 155

be followed by gynæcomastia In the case of a man aged 73 years bilateral gynæcomastia had followed prostatectomy and in one of his hypertrophied breasts true mammary carcinoma supervened afterwards (Petit de la Villeon *Presse méd* 1924 32 832 meeting of the Societe des chirurgiens *de* Paris October 10 1924)

Gynæcomastia and Endocrine Tumours of the Thymus

For evidence that endocrine overfunction of the thymus may give rise to macrogenitosomia with a virilistic tendency *see* F Parkes Weber and M Wohl Macrogenitosomia of the juvenile Hercules type with tumour in the superior mediastinum *Med Press and Circ* 1944 **211** 22 In that paper Mr J E H Roberts kindly permitted me to mention the case of a boy aged 16 years whom he showed me at the Royal Society of Medicine (Clinical Section) on December 10 1943 (*Proc Roy Soc Med* 1943 1944 **37** 157) The boy had bilateral gynæcomastia and somewhat small testes and had been treated by deep X rays for what was probably a large rapidly growing (malig nant) primary thymic tumour mainly in the anterior mediastinum and causing alarming pressure signs As a result of the treatment the tumour had disappeared Skiagraphic examination after six months showed no recurrence The smallness of the testes remained unaltered The enlargement of the breasts which had come on at the time when the thoracic pressure signs commenced (suggesting causal connexion with the tumour) somewhat diminished with the disappearance of the tumour How can one reconcile the mammary feminism which occurred in Mr Roberts case with the macro genitosomia of the virile—muscular or juvenile Hercules—type which was the striking feature in the case described by F P Weber and M Wohl? The difference is probably due less to difference in the thymic hormones at work than to difference in the bodily soil on which the hormones acted Both patients are males but ours is younger (aged 14½ years) than Mr Roberts (aged 16 years) and his body may therefore have been more inclined to react vigorously towards any hormones which promote sexual and general bodily growth Moreover it is quite possible that in our case there was already a specially virile tendency towards precocious sexual and general bodily development whereas in Mr Roberts case there may have been low virility (note the smallness of the testes) and the sexual balance in regard to the mammæ may have been more easily

Gynæcomastia and Endocrine Tumours of the Pituitary Gland

Gynæcomastia with actual secretion of milk has been known to occur in connection with acromegaly, that is to say, with eosinophil adenoma of the pituitary pars anterior O Roth (*Berl Klin Woch enschr*, 1918, 55, 305) records such a case in a man, aged 28 years I do not know, however, of mammary hypertrophy or secretion of milk having ever been observed in males with the basophil adeno mata of the pituitary in Cushing s syndrome

Here I must refer to the occasional occurrence of macrogenito somia in association with non endocrine tumours of the pineal body or the mid brain and hypothalamus which by their position in regard to and their probable stimulation of or pressure on the hypo thalamus, have given rise to macrogenitosomia in boys One such case, admirably described and elucidated by H S Le Marquand and D S Russell (*Royal Berkshire Hospital Reports*, 1934 1935 p 31), was due to a hamartoma or choristoma (a kind of developmental error) occupying the interpeduncular space attached to the right corpus mammillare and the tuber cinereum The most recent case of the kind described by H Cohen J Pennybacker and D S Russell (*Quart Journ Med* 1943, 12, 262) was due to a cystic astro cytoma involving notably the third ventricle and the hypothalamus including the mammillary bodies and causing hydrocephalus and papillœdema

In some such cases however the feministic sign of gynæcomastia has been observed for instance in a boy aged four years with a pineal tumour whose case has been described by Oestreich and Slawyk (*Virchow s Arch* 1899 157, 475)

Gynæcomastia and Endocrine Tumours of the Testis

Primary tumours of the testis arising from the interstitial cells may give rise to macrogenitosomia of the juvenile Hercules or muscular type in boys (cf Rowland Nicholson and Weber *Guy s Hospital Reports* 1929 79 405) But the feministic sign of gynæco mastia has been noted in certain cases of teratoma testis, due in some cases probably to the chorion carcinomatous elements present

Here one may note that injury to a testis prostatectomy castration in early life or testicular atrophy from various causes may sometimes

XII

PROBLEMS OF CORTICAL HYPERADRENALISM[1]

When by analogy with hyperthyroidism the term (anterior) hyperpituitarism had been introduced for pituitary gigantism and acromegaly it became clear after some years that this must be changed to (anterior) eosinophilic hyperpituitarism to differentiate it from (anterior) basophilic hyperpituitarism—Cushing s syndrome or rather Cushing s disease

Should cases of cortical hyperadrenalism likewise be divided into two classes (1) the well known class in which excessive action of the cortical endocrine cells (whether the result of a malignant or non malignant endocrine tumour of the cortex or of mere hyper function of the cortex without any actual endocrine tumour) produces virilism (2) the much rarer cases in which it produces feminism?

In a case shown to me in 1915—a man aged 27 years to which my then surgical colleague Dr zum Busch afterwards allowed me to refer (*Brit J Derm* 1926 28 7)—feminism in the form of bilateral mammary enlargement (a few drops of milky fluid could be squeezed from the nipple of either breast) occurred as the result of an adrenal cortical endocrine tumour I first thought that this was the only example of the kind on record but the publication of the Bittorf Mathias case was earlier (*Virchow s Arch* 1922 236 466) and since then two or three well authenticated analogous cases have been recorded

The question has therefore naturally arisen whether there may be an adrenal cortical hormone (*a*) with a feminism producing function like folliculin as well as (*b*) a virilism producing hormone like testosterone and the active principle of andreioblastomata in females If those who hold this view are correct we already can quote rare instances of feminism producing cortical hyper adrenalism (with or without actual tumour formation) in males (as referred to above) but are there analogous cases in females? May there not be mild forms of feminism producing cortical hyperadrenalism in females (probably without any actual cortical endocrine tumour) to account for some cases of excessive development of the uterus (perhaps with early and excessive menstruation and myomata) and possibly exaggeration of breast development and

[1]Letter in *Brit Med Journ* 1945 1 384

tilted towards the female side (gynæcomastia) by shock action of the rapidly growing thymic neoplasm

Remarks

From this short summary of the somatic effects of endocrine tumours, at least in so far as the production of gynæcomastia is concerned, it would seem at first sight that functioning neoplasms can cause increase of virilism, or occasionally—at least at certain ages and under certain circumstances—exactly opposite effects namely, signs of feminism The precise effect produced by the excess of hormones entering the circulation depends doubtless to some extent on the soil on which they work It is difficult of course to say how much of the effect is due to direct action of the hormones and how much to reaction towards the hormones When the endocrine (hormonic) balance is once upset by the development of a functioning endocrine neoplasm the kind and amount of the somatic effect produced must largely depend on the zygotic make up of the individual (and the special portions of his body concerned), including hereditary tendencies, temporarily modified by age and other circumstances which help to constitute the soil on which the hormones work In the present paper I have limited myself almost entirely to somatic effects on the mammæ

A GLYCOSURIC FAMILY WITHOUT HYPERGLYCÆMIA—
So-called Renal Diabetes[1]

The Mother

Mrs E B, an English woman, now aged 57 (1931), is known to have passed sugar in her urine (between 1 and 4 per cent) for at least forty four years—without hyperglycæmia, polyuria, excessive thirst, or other distinguishing signs of diabetes mellitus. Owing to the absence of polyuria such cases cannot correctly be termed diabetes, at least not according to the original meaning of the term. They can hardly even be termed renal excepting in the sense that the glycosuria is due to a low renal threshold for sugar, which is a congenital developmental condition, as the history of the present family (and some other families) shows. Probably glycosuria till now has never been known to have existed quite so long as forty four years, but the patient is every day breaking her own record, and from the nature of the condition as now admitted it is clear that in others it may last for an equally long or longer time. There is no evidence that it has exercised any injurious influence on the general health of Mrs E B, or that *per se* it ever does so in similar cases.

I first saw Mrs E B on June 18, 1914, when she was 40 years old, on her admission to the German Hospital under my care suffering from acute polyneuritis of uncertain causation; all four limbs were affected, the upper ones much less severely than the lower ones. In the hospital the paralysis began rapidly to disappear, and by July 17 she could walk about a little. By July 30 her tendon reflexes had all returned.[2] The substance excreted was ordinary glucose, but there was neither polyuria nor excessive thirst, and the blood sugar was found to be only 0.083–0.094 per cent. No disease in the thoracic or abdominal viscera was discovered by ordinary examination, and the blood serum gave a negative Wassermann reaction.

The most interesting point in the previous history of the patient was that in 1887, when about 13 years of age, she had been an in-patient at the Middlesex Hospital suffering from tonsillitis. From the medical registrar of that hospital I ascertained that according to the

[1] *Lancet*, 1931, 2, 1

[2] Weber, F Parkes, Acute Polyneuritis in a patient with Chronic Diabetes Mellitus without Hyperglycæmia, St Bartholomew's Hospital Reports, London, 1914, 50, 169

secondary female sex characters? Dr G Samson in a conversation has even suggested to me that the feministic features of so called 'pituitary obesity and Frohlich s dystrophia adiposo genitalis in both boys and girls might conceivably partly be due to excessive formation of such a feminism producing adrenal cortical hormone

It is clear that the above suggestions are only theoretical explanations In the same way, it might be suggested that an active thymic endocrine tumour or delayed involution of a large thymus in a young male might cause either excessive virilism of the macrogenitosomia type, or still more rarely, feminism with gynæcomastia and smallness of testes and penis, and that this might be accounted for by assuming the existence of a virilism producing thymic hormone dominating in the former cases, and a feminism producing thymic hormone in the latter But other explanations seem more probable (Weber and Wohl, *Med Press and Circ*, 1944 **211** 22 Weber, *ibid*, p 155)

saw him on May 19 soon after his return he looked strong and sunburnt his urine contained 4 8 per cent sugar and was free from acetone and diacetic acid His blood sugar (fasting) was 0 091 per cent On May 22 a blood sugar curve was taken and found normal the fasting blood sugar on that occasion being 0 073 per cent

3 A daughter A E B aged 20 years whose urine when tested recently contained 4 3 per cent sugar Her blood sugar curve (June 5 1931) was found to be normal the fasting blood sugar on that occasion being 0 089 per cent She is well grown and the only obvious abnormality about her excepting the glycosuria is that she has a typical nævus anæmicus on her right hand which I demonstrated on June 18 at the Dermatological Section of the Royal Society of Medicine She sometimes has headaches similar to those of her mother

4 A son H J B aged 18 years had 0 3 per cent sugar in his urine when it was tested recently His blood sugar curve on May 29 1931 was normal but on that occasion his urine was free from sugar It seems that he only occasionally has glycosuria Dr George Graham has referred to individuals with true renal glycosuria who pass sugar only after a meal (A miscarriage at the fourth month came (in 1915) between this child and the youngest one)

5 The youngest child a boy A G V B aged 15 years was recently found to be passing urine containing 2 5 per cent sugar His blood sugar curve taken on June 5 1931 was normal the fasting blood sugar on that occasion being 0 084 per cent

Remarks

This family group though consisting of only two generations is interesting because it shows how in cases of the kind the glycosuria may increase the difficulties of diagnosis when any infection or temporary illness occurs Thus in the mother Mrs E B in 1914 the unimportance of the glycosuria was not at first recognized when she was attacked by the alarming acute polyneuritis and was almost completely paralysed

When her son (J W B) had an attack of headache with slight vomiting as his mother sometimes has the discovery of sugar in his urine led (in a New Zealand hospital) to the diagnosis of grave diabetes mellitus he was apparently given to understand that he would fall a victim to diabetic coma if he did not keep to the special diet and continue the insulin injections When I heard of his sup

notes at that time (1887) she was passing 62 to 124 g of glucose in 852 to 1705 c cm of urine daily the specific gravity of the urine being about 1040

In July, 1919 Mrs E B saw Dr W Langdon Brown on account of headaches he informed me that she still passed sugar in her urine and that her blood sugar was within normal limits When I saw her again at the German Hospital on May 19, 1931 her urine was of specific gravity 1036 and contained 3 5 per cent sugar, it gave negative reactions for acetone and diacetic acid The blood sugar (fasting) was 0 096 per cent There can therefore be scarcely a doubt that (as above stated) Mrs E B has had continuous glycosuria since her urine was tested for the first time in 1887 She has lived a hard working life and apart from fibrositic troubles and occasional head aches (possibly of the nature of migraine and sometimes accom panied by retching and if she takes any food, by vomiting) her general health has been good

In regard to Mrs E B s parents they are said to have been first cousins and to have died of pulmonary tuberculosis aged 37 and 58 years respectively I do not know whether either of them or both of them had glycosuria but Mrs E B s two sisters and one brother have not glycosuria However Mrs E B s glycosuria (renal diabetes) has been inherited by some of her children She has had five children all of whom are still living and one miscarriage in the following order

The Five Children

1 A daughter Mrs P aged 26 years who is married and has one child a boy aged 4 years Specimens of urine from both of them examined in May 1931 have been found free from sugar They have, therefore probably escaped the familial glycosuria It should be noted that this Mrs P the eldest child of Mrs E B had a different father than Mrs E B s subsequent children have had all of whom now have glycosuria without hyperglycæmia

2 J W B Mrs E B s eldest son aged 21 years a well developed young man, when in New Zealand during November 1930 com plained of headache accompanied by a little vomiting somewhat similar to his mother s attacks His urine was examined and found to contain sugar He was put on an anti diabetic diet and treated with insulin till his return to England in May 1931 in fact he received insulin injections even during the voyage home When I

XIV

LUTEMBACHER'S SYNDROME, WITH AN ACCOUNT OF A CASE

Developmental and Teleological Explanation of the Condition as the Result of Teleological Adaptive Reaction Towards a Primary Developmental Error[1]

LUTEMBACHER's syndrome is mitral stenosis with a defect in the interauricular septum Following is the clinical account of a case with a developmental and teleological explanation of the condition

Case

The patient is a young man aged 24 years of rather delicate build and looking slightly younger than his age There is a little cyanosis in lips and toes but best marked in his fingers which though not definitely *clubbed have incurved nails* He says that as a child he was always short of breath on even slight physical exertion and was unable to take part in sports or gymnastics At rest he did not notice anything wrong Lately there has been an exacerbation of symptoms owing to increased muscular work He has often had bronchitis and once pneumonia No history of rheumatism No similar trouble known of amongst his relatives He says that he comes of a healthy family

Heart—Apex beat in 5th left intercostal space ½ in to left of nipple line The impulse is somewhat heaving and after exertion a slight thrill has sometimes been felt over a great part of the cardiac area On auscultation there is a decided presystolic murmur ending with a sharp first sound this murmur is not localized to the apex *as it is in some typical cases of mitral stenosis but is best heard* over an area nearer to the middle line There is no other murmur Pulse about 60 Brachial blood pressure 100 60 mm Hg Blood count *hæmoglobin 100 per cent erythrocytes 5 000 000 colour index 1 0* Erythrocyte sedimentation and electrocardiogram show nothing abnormal By ordinary examination of the lungs abdominal viscera and urine *there is nothing abnormal no enlargement of liver* or spleen or superficial lymphatic glands no abnormality in sexual development

X ray examination of the heart (by Dr F G Wood *to whom we* are indebted) The heart is enlarged to the left and shows prominence of the left ventricle The aorta is small The root shadows are

[1] *From a paper with D Gertrud Samson M d P and Cir* 1945 213 392

posed dangerous illness, I naturally suspected that his glycosuria would turn out to be of the same nature as his mother s

The case of the mother (Mrs E B) is by itself of great interest, since it is clear that she must have been passing sugar in her urine for forty four years without being any the worse for it Nevertheless from the elaborate Study of Orthoglycæmic Glycosuria with Particular Reference to its Heredıtability, by Dr Urban Hjarne (translated by Carl Westman and published in Stockholm in 1927), a copy of which has been lent me by Dr Graham, it appears that true diabetes mellitus may occur in renal glycosuria families In the present family the fact that the parents of Mrs E B were first cousins should be noted, though it is not known whether either of them had glycosuria

I am indebted to the assistance of my house physician Dr M Scholtz and without the help of Dr George Graham, I should not have been able to settle the nature of the glycosuria in Mrs E B in 1914

This account may prove of interest in regard to similar small family groups that are certain to turn up from time to time in England and abroad Personally it may save me much trouble, as my printed accounts of rare or doubtful cases have sometimes done, by way of replying to doctors under whose observation the individuals themselves or members of their families subsequently fall

(This account was published in 1931 and the ages given are those for that year The mother (Mrs E B) and all her children are still living excepting one son who was lost in the war — F P W, February 1946)

somewhat deficient flow of blood into the aorta during intra-uterine and early extra-uterine life. The hypertrophy of the left ventricle may be explained as due to increased myocardial activity resulting from reactive endeavour to force more blood into the hypoplastic aorta. (This explanation is not at variance with the fact that in rare cases of *acquired* pure mitral stenosis of rheumatic origin the left ventricle is not hypertrophied.) What is somewhat loosely termed "back pressure" may be supposed to favour the occurrence of enlargement of the left auricle, the pulmonary blood vessels, the pulmonary conus, and may even favour the defective closure of the foramen ovale. Moreover, the relatively good prognosis *quoad vitam* in Lutembacher's syndrome seems to us to accord with the above views. The rather delicate or undeveloped or (in rare cases) even infantile and dwarfic condition of some of the patients may well be connected with the aortic hypoplasia, as has been suggested. We would compare it to what has been termed "mitral dwarfism" (cf. F. P. Weber, 1913) or "cardiac dwarfism" in cases in which the mitral disease, whether congenital or acquired, has been present in early childhood. This has been called "angioplastic dwarfism", the dwarfism of the whole body being regarded as a conservative adaptation towards the defective cardiac and arterial conditions—an attempt of nature to limit the growth of the patient in accordance with the limited arterial blood supply. One might term the process a "conservative hypoplasia" of the whole body.

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increased and show marked vascular pulsation on screening There is some prominence of the pulmonary conus A barium swallow shows no definite evidence of enlargement of the left auricle In the lateral view the pulmonary artery is seen to be enlarged

Diagnosis

In the present case the presystolic murmur of mitral stenosis is typical, excepting that it is best heard not at the apex but nearer to the sternum than it is in ordinary rheumatic cases of mitral stenosis The other features are likewise typical excepting that X ray examination during barium swallowing gives no definite evidence of enlargement of the left auricle There is however enlargement of the vascular shadows at the roots of the lungs with some prominence of the pulmonary conus We know that necropsies on patients who have presented the clinical features of Lutembacher s syndrome have revealed mitral stenosis and an interauricular septal defect which is nearly always a patent foramen ovale—very rarely a persistent ostium primum or persistent ostium secundum Could our case be anything other than Lutembacher s syndrome? One can only think of the possibility of an interventricular septal defect (maladie de Roger), but we have never heard of this congenital interventricular defect being associated with mitral stenosis That most cases of Lutembacher s syndrome have been in females is of course, no argument against the genuineness of our present case in a male

Developmental and Teleological Explanation of Lutembacher's Syndrome, as the Result of Teleological Adaptive Reaction Towards a Primary Developmental Error

It was formerly the fashion in Great Britain to maintain that all cases of mitral stenosis are of rheumatic origin whether a history of rheumatic fever can be obtained or not But in most patients with Lutembacher s syndrome, as in the present case a rheumatic history is entirely wanting Moreover to our minds a general consideration of the condition (including necropsy accounts) forces one to regard the mitral stenosis as congenital (developmental)

If we admit the presence of a primary congenital (developmental) obstruction at the mitral orifice hindering the full entry of blood into the left ventricle and aorta the aortic hypoplasia can be well explained as a secondary developmental defect connected with

tremely rare and fatal condition described by Guglielmo which by description seems as if it might be a very acute erythroblastæmic variety of myeloid leukæmia in infants In reactive compensatory polycythæmia due to insufficient oxygenation of the red blood cells erythroblastæmia is rarely found Such polycythæmia includes the polycythæmia of high altitudes the compensatory polycythæmia in some congenital cardiac malformations and occasionally in acquired chronic valvular disease and the polycythæmia connected with various types of pulmonary obstruction to the circulation of blood through the lungs Regenerative compensatory erythropoiesis associated with erythroblastæmia is seen after hæmorrhage and in various types of infective toxic or metabolic anæmia

There is no erythroblastæmia in non regenerative (aplastic) anæmias but in some cases of clinical aplastic anæmia the fact that there are no nucleated red cells or other signs of active compensatory hæmopoiesis in the circulating blood does not prove that erythro poiesis is not going on in the bone marrow it proves only that red cells are not entering the circulating blood from the bone marrow The diagnosis in such cases nowadays may be greatly aided by sternal puncture

Among the rarer anæmias of uncertain origin in which occasion ally during the rapid regenerative period there may be erythroblast æmia is the acute hæmolytic anæmia of Lederer Nucleated red cells notably megaloblasts may constitute a striking feature of the blood during regenerative blood crises in true pernicious (Addisonian) anæmia The severe blood rises in familial hæmolytic (acholuric) jaundice and even in the much rarer puzzling cases of supposed acquired hæmolytic jaundice are accompanied by erythro blastæmia

Erythroblastæmia or as Janet Vaughan and others say leuco erythroblastic anæmia often accompanies secondary neoplastic infiltration of the bone marrow It is hard to be sure whether this erythroblastæmia is part of an attempted erythropoiesis to com pensate for destruction of the bone marrow by the new growth or whether it is to be regarded (at least in part) as due to some other kind of excitation of the erythroblastic elements in the bone marrow by direct contact with the infiltrating neoplastic cells These two causes probably work together in various proportions in different cases Billings and Capps (1903) mentioned a case of neoplastic infiltration of the bone marrow in which the blood count showed

XV

ERYTHROBLASTÆMIA

And its Value in the Diagnosis of Neoplastic Infiltration of Bone-Marrow[1]

ERYTHROBLASTÆMIA is present when ordinary blood counts show nucleated red cells in the circulating blood I say ordinary blood counts because occasionally, by extraordinarily long searching, probably especially after unaccustomed severe muscular exercise, one or two nucleated red cells may be found in the circulating blood of normal adults Erythroblastæmia includes all primary or secondary leuco erythroblastic anæmia i e all cases in which the blood picture shows anæmia and immature red cells (erythroblasts) and immature white cells (myelocytes) Erythroblastæmia may also occur without leuco erythroblastic anæmia

Ætiology

The blood of newborn especially of premature infants usually contains a moderate number of nucleated red cells during the first week of extra uterine life Many nucleated red cells are likely to be present in the blood of newborn infants with inherited syphilis—a manifestation of the infantile hæmopoietic reaction towards the infection Various other infections and toxic conditions in children are associated with reactive or regenerative erythroblastæmia Among these one must especially remember Von Jaksch s anæmia (pseudoleukæmia or infantile type of splenic anæmia) Erythro blastæmia is a feature of fœtal erythroblastosis (including icterus gravis neonatorum and congenital universal anasarca) and Cooley s erythroblastic anæmia a rare familial developmental abnormality mainly observed in families of Italian or Mediterranean origin settled in America

Nucleated red cells may sometimes but not always be found in the blood when there is excessive erythropoiesis whether primary i e of unknown or of uncertain causation or secondary i e reactive, to compensate either for insufficient oxygenation of the red blood cells or for some known kind of anæmia The excessive erythro poiesis is primary or of unknown causation in erythræmia or primary polycythæmia mostly with definite splenomegaly of the Vaquez Osler type and in acute erythræmic myelosis of infants the ex

[1]After the *Lancet* 1940 1 1077

probably generally enlarged in such cases, but whether there is ever a myeloid (hæmopoietic) change in the spleen, as there is apparently in some of the cases of the Albers Schonberg type I do not know In such cases the total leucocyte count is increased in the above mentioned case it was 15 200–51 200 per c mm According to Naegeli (1923) the changes due to neoplastic invasion of the bone marrow include great increase in the leucocyte count often with the presence of immature cells, and persistent presence of nucleated red cells, the normoblasts being more numerous than the macroblasts which always show much polychromasia As regards differential diagnosis by the blood picture from pernicious anæmia it must be remembered that the colour index may sometimes be up to at least 1 in neoplastic cases

In some cases of primary developmental marble bones (Albers Schonberg type) there is a leuco erythroblastic anæmia but it does not seem to be proved that this and the accompanying splenomegaly are evidence of a hæmopoiesis to compensate for the diminution in the total amount of bone marrow A rare leuco erythroblastic anæmia associated with splenomegaly and often with a sclerosis of the bone marrow has been discussed by McMichael and McNee (1936) and others and called by Hickling (1937) chronic non leucæmic myelosis The difficulty in understanding the pathology of these cases is increased by the fact that cases of true leukæmia have been observed in which a sclerosis of the bone marrow was found at necropsy Erythroblastæmia may be found in all kinds of leukæmia both in myelosis including erythroleukæmic cases and in lymphadenosis and even in aleukæmic and leucopenic forms In myelosis and erythroleukæmic cases the erythroblastæmia may be regarded a part of the primary disorder of hæmopoiesis but in lymphadenosis (lymphatic leukæmia) the terminal erythroblastæmia may perhap be due to a compensatory activity in the remaining erythropoietic marrow when much has been destroyed by the lymphoid infiltration

Neoplastic Infiltration of Bone-Marrow

Erythroblastæmia is of value in the diagnosis of cases in which skiagrams show a symmetrical uniform osteosclerosis in the pelvis In such cases the question may arise whether the sclerosis, in spite of its being diffuse and uniform without any obvious localized foci is due to secondary neoplastic infiltration or is an example of what by some has been called osteitis condensans ilii Garre s sclerosing

over 90 000 nucleated red cells per c mm of blood, but the number may be much higher The neoplastic infiltration is nearly always secondary to carcinoma I do not think that any erythroblastæmia has been found in most cases of primary tumours of the bones (sarcomata) or of the bone marrow, but nucleated red cells have been mentioned in blood counts in myelomatosis (multiple myeloma)

It is not clear why in some cases of secondary neoplastic infiltration of the bone marrow new bone is formed instead of bone being absorbed Such osteoplastic results are relatively rare, the patients are mostly men with prostatic carcinoma and the prostate need not be enlarged Apparently in such cases the prostatic carcinoma pours into the blood stream millions of carcinoma cells which are held up mostly in the bones and bone marrow the innumerable metastases each consisting generally of only a few cells Obviously the cancer cells must also be carried in large numbers to other tissues where apparently they atrophy Perhaps this may explain some of the rheumatic like pains and general malaise of which the patients complain besides their more definite bone pains

An example of the predilection of metastases for certain sites is the well known predilection of metastases from suprarenal neuroblastoma in children (the Robert Hutchison type) for the orbits and skull The experimental work of Takahashi (1915 16) and others who injected intravenously carcinomatous or sarcomatous material showed that a large proportion of the injected neoplastic cells disappeared after undergoing vacuolation surrounded by leucocytes Although the capillaries of the lungs formed a fairly efficient filter, some tumour cells passed through the lungs and produced metastatic tumours in various parts of the body showing a predilection for certain sites

The osteoplastic change increases not only the weight but also the thickness of the affected bones (prepared as museum specimens) I have called such bones the secondary marble bones (Weber 1935) in contrast with the rare developmental (mostly congenital) primary *marble bones of Albers Schonberg In a case of the kind that* I described in 1909 the osteoplastic change in the bones (specimens of which are in the museum of the Royal College of Surgeons) was typical but the prostate not being enlarged the diagnosis was not made at first even after necropsy In this patient s circulating blood the counts showed 622–121,856 nucleated red cells per c mm The spleen was somewhat enlarged and not soft weighing 350 g It is

glands There was sclerosis in both iliac bones one rib and some vertebral bodies and in the left ilium there was a soft metastatic deposit which microscopy proved to be carcinomatous Microscopy of a metastasis in the liver showed adenocarcinoma and there could be no doubt that the whole condition was secondary to the original gastric carcinoma

For help in the examination of this case I thank my then house physician Dr H Huber

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osteitis seems to be a chronic low grade infection of the lymphatics of the bones and persists in spite of deep X ray treatment In Bársony and Polgar s cases (1928) of osteitis condensans ilii the sclerosis was not always strictly confined to the ilium, in their type of case the course seems to be benign and apart from sacral and radiating pains, clinical signs (except radiological) are absent Rendich and Shapiro (1936) think that nothing certain is known about the true nature of this condition, known to radiologists as osteitis condensans ilii Shafer (1938) suggests that there are many causes including the action of fluorides, phosphorus in small doses (large doses have the reverse effect), and lead

Case Record

A man, aged 53 was readmitted to hospital on May 30, 1939, after having had in February 1937 a resection of the pyloric region of the stomach for carcinoma, the diagnosis being confirmed by microscopy On readmission in 1939 he complained of pains like sciatica on the left side together with other pains, of about two months duration In the hospital he rapidly lost ground and lower back pains were severe

The skiagrams of the skeleton showed a sclerosis of the pelvis such as I have already described A great authority on abnormal conditions of bones who kindly examined the skiagrams thought that the density was too uniform for neoplastic metastases More over diffuse uniform secondary infiltration of bones from gastric carcinoma must be rare A blood count on June 18 1939 gave the following results —

Red cells, 2 800 000 white cells 19 000, hæmoglobin 44 per cent colour index 0 8 polymorphs 84 per cent lymphocytes, 9 per cent, monocytes 5 per cent eosinophils 1 per cent, myelocytes 1 per cent

Some basophilic punctation of erythrocytes was noted and there were many megalocytes and decided polychromasia Four nucleated red cells (normoblasts) were seen in counting 100 leucocytes i e there were 760 nucleated red cells per c mm This leuco erythro blastic anæmia suggested that the radiographic appearance of the pelvis was due to metastatic carcinomatous infiltration which was indeed found at necropsy a week later

No recurrent carcinoma was found in the stomach but there were macroscopic metastases in the liver and various abdominal lymph

plasias of the skeletal (bone and cartilage) muscular, vascular and nervous systems, and many minor conditions, including inherited abnormalities of the skin and its appendages food idiosyncrasies and allergic peculiarities It is almost certain that many diseases which are rarely obviously inherited—such as hypertrophic pyloric stenosis (which may occur occasionally in twins or recurrently in more than one child of the same parents) and Hirschsprung s megalo colon congenitum and aortic isthmus stenosis—also really belong to the group under consideration [1] All inborn constitutional diseases belong to the congenital developmental group, even when their manifestations are delayed till long after birth till puberty middle age or even later It is because the manifestations are often delayed till long after birth that I prefer to speak of this group of diseases as the congenital developmental group and not as the congenital group

Known hereditary or familial incidence may often be absent in diseases and abnormalities of the congenital developmental class but its occasional presence is sufficient to stamp the disease or abnor mality as belonging to the class * Thus the puzzling disease lipo dystrophia progressiva apparently belongs to the class and seems to be a dysbiotrophy' (if I may use the term instead of abio trophy of Gowers) of the subcutaneous fat over the head and upper part of the body chiefly affecting females L Barraquer-Ferre has lately narrated the case of a female whose mother and maternal grandmother were likewise affected The disease though potentially present at birth may be delayed in its appearance long enough to allow of a female not being prevented by her shrunken death s head like face from finding a mate Some would probably prefer to express themselves by saying that the lipodystrophia was potentially present at birth as a congenital tissue inferiority (Gewebsminderwertigkeit)

I —Examples of the Familial Incidence of Hepatic Cirrhosis not Due to any Known Exciting Agent of the Disease

Various cases of familial hepatic cirrhosis have been published

At the Royal Society of Medicine (Section for the Study of Disease in Children) in February, 1934 Professor F Langmead[2] demons

* The possibility of Mendelian recessive heredity and parental consanguinity must be remembered

XVI

INBORN AND FAMILIAL TENDENCY TO THE DEVELOPMENT OF HEPATIC CIRRHOSIS[1]

CASES of hepatic cirrhosis in children, not due to alcohol or congenital syphilis or any known cause of cirrhosis, are usually regarded as the manifestation or one of the manifestations of a congenital developmental disease and the occasional familial incidence of cirrhosis has often been adduced in support of this view In this paper I shall shortly discuss the data in favour of there being an inborn tendency to hepatic cirrhosis (a congenital tissue or organ inferiority of the liver as Professor Brouwer would say destined to manifest itself by obvious changes in postnatal life, with or without known exciting causes) and shall arrange my remarks under two headings (I) examples of the familial incidence of hepatic cirrhosis, in which the cirrhosis has not been due to any known exciting cause such as alcohol or syphilis or in which an inborn familial tendency to the disease may be presumed because an exciting cause such as alcohol, though present in one of the affected members of the family, was absent in others (II) examples of hepatic cirrhosis accompanying and probably constituting a part of acknowledged diseases of the congenital developmental class

But first I must explain what I mean by *diseases of the congenital developmental class* Under congenital developmental diseases and abnormalities I include all truly inborn abnormalities and constitutional diseases whether obvious at birth or manifesting themselves later at various ages Amongst the more easily recognized ones are hæmophilia hæmolytic (acholuric) jaundice and some other familial abnormalities of the blood (and hæmopoietic system) alkaptonuria congenital porphyrinuria and other inborn abnormalities of metabolism such as Gaucher s disease the Niemann Pick disease, amaurotic family idiocy familial cutaneous xanthomatosis the Hand Schuller Christian lipoid granulomatosis von Gierke s hepatomegalic glycogen storage disease etc renal glycosuria (apparently harmless in itself) familial optic nerve atrophy and other diseases dysplasias and dysbiotrophic conditions in which the eyes are affected numerous hereditary diseases and dys

[1]From the *Lancet* 1936 1 305 Some remarks on this subject which are here amplified were made by Dr Parkes Weber in the discussion on Prof B Brouwer s paper on the Spleen the Liver and the Brain at the meeting of the Section of Neurology of the Royal Society of Medicine on January 16 1936

of the brain combined with a cirrhosis of the liver which has been usually latent during life and first discovered at the post mortem examination Familial incidence in this rare disease has been emphasized by Wilson himself as well as by later authors The evidence seems to me to point to the disease being most probably a combined dysbiotrophy of the lenticular nuclei and the liver, and the hepatic constituent of the combined condition in some cases does give rise to obvious clinical symptoms so as to be recognized as a form of familial cirrhosis even during life [14] In some cases the lenticular nuclei or the liver may be only slightly affected but it seems very unlikely that any of the above mentioned cases of familiar hepatic cirrhosis in children were of the nature of incomplete Wilson s disease with the liver only affected

Hæmochromatosis —The occurrence of hepatic cirrhosis (pigmentary cirrhosis of the liver) as a part of hæmochromatosis or bronzed diabetes is too well known to need insistence The site of the greatest visceral changes varies in different cases and the characteristic liver changes may occur even without very marked cutaneous pigmentation The occasional familial incidence of the disease has been pointed out by J H Sheldon [15] R D Lawrence [16] and others, so that hæmochromatosis must be classed amongst the rare inborn abnormalities of metabolism such as alkaptonuria, pentosuria, cystinuria congenital porphyrinuria the inborn abnormalities of lipoid metabolism etc which I have above referred to Indeed a special analogy may be pointed out in regard to von Gierke s hepatomegalic glycogen storage abnormality inasmuch as in the latter disease different viscera (e g the heart) may be specially involved in different cases

Erythræmia —Though I think that erythræmia of the Vaquez Osler type is like the leukæmias due to a neoplastic change in the bone marrow a familial incidence of the disease has been reported in quite a number of cases [17] It may be presumed to develop (under the action of unknown agents) in individuals having an inborn constitutional predisposition Hepatic cirrhosis is a recognized though only occasional complication of erythræmia and seems in some cases to occur independently of any special agent such as phenylhydrazine which may have been used in the treatment [18]

Telangiectasia of the Osler type —Very many valuable papers have been written on this disease including regular monographs with copious bibliographies by H I Goldstein, who was I believe the

trated cirrhosis of the liver with splenomegaly in three brothers aged 9, 11, and 13 years respectively In the boy, aged 11 years, the diagnosis was subsequently confirmed by microscopic examination ('biopsy'), which showed typical multilobular cirrhosis of the liver Langmead referred to Byrom Bramwell s account (1910) of a family with hepatic cirrhosis [4] Byrom Bramwell s patient, a boy, aged 9 years, had ascites œdema jaundice, fever, and a large liver, and the necropsy showed typical hob nailed cirrhosis Three other members (girls) of the family of seven apparently died from hepatic cirrhosis Langmead also mentioned J Szanto s[5] three cases of multilobular cirrhosis of unknown origin, with splenomegaly, in a family of ten In one of these cases the diagnosis of hepatic cirrhosis was confirmed by necropsy (a boy aged 15 years) who likewise had genital hypoplasia

F J Poynton and *W G* Wyllie[6] in 1926 described two cases of congenital familial hepatic cirrhosis of unknown ætiology in a brother and sister aged 9 years and 4 years respectively but the diagnosis of von Gierke s hepatomegaly (hepatomegalia glycogenica) was subsequently suggested [7]

In 1903 I recorded the necropsy on a girl aged 14 years with biliary cirrhosis (Hanot s disease) of the liver [8] Her sister was said to have died at the age of 10 years with similar symptoms J Dreschfeld[9] met with hypertrophic hepatic cirrhosis in two brothers, one of them was a drinker and the other temperate Sir William Osler[10] mentioned two brothers in America affected with Hanot s cirrhosis Boinet[11] wrote of a family in which the father and two children had biliary cirrhosis (Hanot s type) and three other children had enlarged spleens J Finlayson[12] spoke of three brothers and a sister two of whom had cirrhosis of Hanot s type another had enlargement of the liver and spleen with icterus and the remaining one had slight jaundice Hasenclever[13] recorded an instance of three members of one family a boy and two of his sisters, having typical hypertrophic biliary cirrhosis

II —Examples of Hepatic Cirrhosis Accompanying and Probably Constituting a Part of Acknowledged Diseases of the Congenital Developmental Class

Progressive lenticular degeneration (Kinnier Wilson s disease) —Wilson s disease is a chronic progressive degeneration of the lenticular nuclei

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[19]Osler W Principles and Practice of Medicine London 1905 6th ed p 5 1
[1] Boinet Arch gen d méd Paris 1898 181 385
[2]Finlayson J Glas ow Hosp Rep 1899 2 39
[13]Hasenclever Berlin klin Woch 1898 35 997
[14]Cf the cases described by Stanley Barnes (Proc Roy Soc Med 19 4 18 Sect Neurol p 34) in one of which (Case 3) the hepat c affection seems to have preceded the lenticular affection Cf al o Lhermitte and Muncie *La Cirrhose familiale splénomegalique forme hépatique de la dégénération hépato lenticulaire Presse méd* 1929 37 1495 Compare however Luthy F *Deut Zeits f Nervenheilk* 193 123 101 and Siemerling E and Jakob A *Ibid* p 18
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[20]Weber F P *Brit Journ Child Dis* 1924 21 198 Sir William Osler s first paper was published in the *Johns Hopkins Hosp Bull* 1901 12 333
[1] van Bogaert L and Scherer J H *Ann de méd* 193 38 290

first to call it the Rendu Osler disease' by which name it is now known in France In many cases though in far from all, there has been striking hereditary incidence I was fortunate enough to be able to describe a typical familial example in 1907[19], and in 1924 [9] I alluded to the possible analogy and association of the telangiectatic condition of the skin and mucous membrane of the nose and mouth with certain hæmorrhagic telangiectatic conditions in the stomach intestines kidneys or lungs In fact it is quite possible that in rare cases the typical cutaneous telangiectases may be altogether absent Very few complete post mortem examinations have been published, but recently Ludo van Bogaert and J H Scherer [1] found hepatic cirrhosis present in a typical familial case of the Rendu Osler type of telangiectasia From what I remember of the progress of the patient I described in 1907 there may well have been visceral disease and perhaps hepatic cirrhosis present at the end I have been told of an as yet unpublished case in which hepatic cirrhosis was found at the post mortem examination so it was also in a remarkably atypical case the liver and spleen from which were (January 13 1936) demonstrated by Mr R Davies Colley at the Medical Society in London The telangiectasia in this disease must be regarded as due to a congenital developmental dysplasia of the small blood vessels potentially present at birth though often not manifesting itself by obvious changes till after puberty What is the relationship of the hepatic cirrhosis when present? Is it the result of an associated developmental dysbiotrophy of the liver i e a congenital tissue or organ inferiority in the sense intended by Professor B Brouwer and others? The subject is complicated by the well known fact that in advanced or active hepatic cirrhosis there is a tendency for the patient to develop cutaneous telangiectases on the face and hands notably those of the spider like type as I have had occasion to observe

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Large parietal foram na n the skull may certainly be hereditary if rarely so Cf Greig D M *Edn Med Jo r* 19 7 n s **24** 629 Weber F P and Schwar E *Proc Roy Soc Md* 1935 36 **29** 1 Goldsmith W M *Journ of H redity* 19 **13** 69

[2]Barraquer Ferre L *Pr ss méd* 1935 **43** 167

[3]Langmead F *Proc R y S c Med* 1934 **27** 939

Bramwell B *Clin Studies* 1910 **8** 347 See also later paper by B rom Bramwell (*Edn Med Jou n* 1916 n s **17** 90) where he uggest that such cas of familial c rrhosi of the liver may be all ed to W lson s progre e lent cular deg nerat on

[5]Szanto J *Monats f Kinderheilk* 19 7 **36** 393

[6]Poynton F J and Wyllie W G *Arch Dis Childhood* 1926 **1** 1

[7]Ellis R W B *Proc Roy S c Med* 1935 **28** 1180

[8]Weber F P *Edn Med Journ* 1903 n **14** 114

blood as if the threshold for its elimination or catabolism were high The mere excess of blood bilirubin in the blood, of course, does no harm, though it makes the blood plasma too yellow and produces the jaundice and causes a highly positive indirect van den Bergh reaction Is it possible that this hyperbilirubinæmia in our present case is the sole obvious result of a new gene mutation of germ cells which has not (yet) manifested itself in the children and grandchildren because it is not a Mendelian dominant like ordinary familial hæmolytic (acholuric) jaundice is?

Postscript—The man died on October 19 1946 in the Archway Hospital Highgate after thrombotic softening in the basal ganglia of his brain and pneumonia He would have been 80 years old on November 25 1946 Owing to the kindness of the Medical Superintendent (Mr J M Milloy) Dr J M Alston and Dr A B Bratton and Dr S H G Robinson I was able to include clinical and pathological data as well as an account of the necropsy findings (Dr A B B and Dr S H G R) in a summary of the whole case, headed A New Type of Congenital Life long Jaundice (*Medical Press* 1946 216, 440) I concluded — One cannot now ascertain whether his production of blood bilirubin had been excessive or not nor whether there was a damming up of blood bilirubin in the blood (high threshold for elimination or catabolism) It seems probable however that there was such a damming up of blood bilirubin as the essential cause of the life long jaundice

XVII

CONGENITAL JAUNDICE IN A MAN AGED 77[1]

I HAVE just seen a man who has been more or less strikingly jaundiced all his life and who was 77 years of age on November 25 He enjoys good health has hardly ever required medical aid of any kind, and continues at work—helping a married son with whose family he lives I first examined him (in connexion with a life assurance question) in 1917, and from time to time have demonstrated his case at the Royal Society of Medicine (*Proceedings Clinical Section* 1917 **10** 13 1928 **21** 3, 1938 **31** 39) He has scars from leg ulcers (1910) considerable deafness (old otosclerosis) and slight nystagmus The blood bilirubin has, of course, been found in excess in the blood serum (negative direct Hijmans van den Bergh reaction), but the urine has always been found free from bilirubin and from excess of urobilin and urobilinogen There has never been any anæmia or enlargement of spleen or liver No abnormal fragility of the erythrocytes (towards graduated sodium chloride solutions) has been discovered The size and shape of the erythrocytes have never been sufficiently studied to enable one to exclude excess of spherocytes Anyhow the case seems to be a very unusual one of congenital hæmolytic (acholuric) jaundice, arising doubtless from a germ cell mutation—possibly a new one as there is no other example of jaundice in the family The jaundice has not been transmitted to any one of his four children

I am anxious to ascertain whether medical readers know of a case similar in all respects I might mention that in the hæmolytic (acholuric) family which I recorded with G Dorner (*Lancet* 1910, **1**, 227) the first ancestor known to have been affected was a man who had been yellow all his life and died at 76 (wrongly printed 70) as a result it was said of leg ulcers

From the short data given above it appears that the present case is one of congenital idiopathic hyperbilirubinæmia—the bilirubin in the blood being of course blood bilirubin, which is probably the the same as what Virchow called hæmatoidin—differing however from the hyperbilirubinæmia of the well known cases of familial hæmolytic (acholuric) jaundice notably by the absence of excess of urobilin or urobilinogen in the urine I suggest that the blood bilirubin in this case is in some way dammed back in the circulating

[1]After *Brit Med Journ* 1943 **2** 690 and 763 (letters)

enlarged, but the liver could be felt a finger breadth below the costal margin in the right nipple line I was uncertain whether there was not a little free fluid in the peritoneum

My next note was in June, 1933 when she was readmitted to hospital with an abdominal swelling which seemed to be an enormous and hard liver the lower *bulbous* portion of which reached down to the pelvis and projected in the right iliac region The spleen could not be felt *There was no ascites or subcutaneous oedema* There were two or three minute spider like telangiectases on the hands, as there not rarely are in cases of hepatic cirrhosis The patient was moderately jaundiced, and her urine contained bilirubin and some excess of urobilin and urobilinogen and a few granular tube casts She was decidedly anæmic (erythrocytes 3 560 000) and the sedimentation of the erythrocytes was too rapid (about ½ hour *instead of over an hour which was the normal for the method employed*) Since I had last seen her (in October 1931) she had been generally more or less jaundiced and had had nose bleeding two or three times *Menstruation had not yet commenced*

Various examinations were made in June 1933 Uroselektan examination of the ureter and renal pelvis showed nothing definitely abnormal on either side The hepatic function test after Morawitz (*see* R Mancke and K Rohr *Deutsch Arch f klin Med*, 1931 **172** 278) was positive for hepatic insufficiency The blood bilirubin was estimated by Dr R Seifert as 4 6 mgm per cent Blood sugar (fasting) 0 1 per cent The blood serum cholesterol (twice estimated by Dr R Seifert) was 77 84 mgm per cent that is to say there was hypocholesterolæmia instead of hypercholesterolæmia but according to J P Peters and D D Van Slyke (*Quantitative Clin Chem* 1931 **1** 247) there may be hypocholesterolæmia in late hepatic cirrhosis as an expression either of some kind of secondary infection or of cachexia Blood serum calcium 10 3 mgm per cent The Rumpel Leede (capillary resistance) test gave a negative response The Wassermann and Meinicke reactions were again negative

The patient who said she felt better was allowed to leave the hospital early in July but was *readmitted* (then aged 15 years) in October of the same year (1933) with considerable cutaneous pruritus in addition to deep jaundice and with slight ascites as well as the great abdominal swelling already mentioned The blood serum icteric index (after Meulengracht) was as high as 99 and owing to the complete absence of urobilinogen and urobilin from the urine it was clear that no bile could be entering the intestine

XVIII

CYSTIC DILATATION OF THE COMMON BILE-DUCT[1]

THE patient, a girl, was 12 years old when shown by F Parkes Weber and M Scholtz on April 10 1930 at the Royal Society of Medicine, Section for the Study of Disease in Children under the heading, 'Idiopathic Hepatic Cirrhosis with Recurrent Jaundice The child was somewhat fat The liver was *considerably enlarged and bulging,* reaching down to the umbilical level There were a few telangiectases on the face She had been admitted to hospital on February 6, 1930, with slight jaundice of obstructive type there was a positive direct Hijmans van den Bergh s reaction for bilirubin in the blood serum The history was that she had had recurrent or remittent jaundice and frequent epistaxis during the preceding 14 months, she had never had hæmatemesis There was no definite enlargement of the spleen and certainly none of the superficial lymphatic glands The blood serum gave negative Wassermann and Meinicke reactions The urine contained some excess of urobilin and urobilinogen but no bili rubin probably the attack of jaundice was disappearing The galactose test showed some impairment of hepatic function The resistance of the erythrocytes towards graduated hypotonic sodium chloride solutions was within normal limits There was nothing special in the family history

In regard to the diagnosis it should be mentioned that the cutaneous reaction to an echinococcus antigen was negative Under dietetic and saline treatment the jaundice gradually disappeared

In the summer of 1931 there is a note that during the last years the patient had certainly been subject to occasional attacks of pain in the upper abdomen more or less of hepatic distribution lasting two or three hours and followed by temporary increase of her permanently slight icteric tinge Apparently with the painful crises there was sometimes vomiting By X ray examination five and eight hours after intravenous injection of tetragnost there was no evidence of gall stones in the gall bladder (which was faintly outlined in the skiagrams) It was thought that cholelithiasis could not be the cause of the hepatic pains In October 1931 I made a note that the patient was then a big well grown girl inclined to be fat, without any trace of jaundice the spleen was apparently not

[1] After *Brit Journ Child Dis* 1934 **31** [illegible]7 and 113
[2] F P Weber and M Scholtz *Proc Roy Soc Med* (Child Sect) 1930 **23** 69

bile duct was not dilated and not stenosed, the distance (with slight stretching) from the papilla of Vater to the opening of the non dilated portion of the common bile duct into its dilated portion (the 'cyst') was 4 cm, and the non dilated portion had evidently been closed during life by pressure from the tensely dilated portion of the duct

The cyst like dilated portion of the choledochus had a thick tough wall which was adherent to the parietal peritoneum by fresh fibrin at the site of the perforation Most of it was lined by a layer of blackish bile pigment From the 'cyst' a dilated and hypertrophied short cystic duct led to the gall bladder The diameter of the orifice of the cystic duct was 2 cm that of the hepatic duct (also somewhat enlarged) was 2½ cm The latter was separated from the orifice of the cystic duct by a ridge, which was 21½ cm away from the junction of the non dilated portion of the common bile duct with the dilated portion

The spleen was enlarged (as it generally is in cases of chronic hepatic cirrhosis), weighing 450 grm Nothing of special importance was noted in the other organ

Microscopic Examination —The liver showed a rather fine multilobular cirrhosis with very little small cell infiltration There was likewise not much apparent increase of bile canaliculi The wall of the cyst (dilated portion of the common bile duct) was of fibrous tissue covered by peritoneum externally internally there was no epithelial lining but in parts there was a lining of inspissated bile or rather bile pigment Mr T W P Lawrence finds that the spontaneous rupture of the cyst wall was due to colliquative degeneration of the fibrous tissue, apparently of ischæmic origin

The Nature of the Hepatic Cirrhosis —It seems to me not quite certain that the cirrhosis is in the present case is of merely biliary obstructive nature but I have no doubt that it may be so for it resembles that observed in a recent adult case [3] which was undoubtedly secondary to post operative stenosis of the hepatic duct In that case as in the present one and most other cases of biliary obstructive jaundice the arrangement of the fibrotic process in the hepatic parenchyma was by no means strictly unilobular and in that case also as in the present one (in which however the cirrhotic process is more advanced) there was very little microscopical evidence of active inflammatory reaction In a paper reviewing the whole subject in

[3] F P Weber and W Wesswange *Med Press and Circ* 1933 187 327

The pale fæces contained no urobilin, but a little urobilinogen (which admittedly may be present in the fæces from cases of complete biliary obstruction) The greatly distended abdomen was covered with cutaneous striæ

Under treatment by very small injections of insulin, by glucose by the mouth, and a little digitalis, the patient's general condition improved for a time the jaundice diminished, and a little urobilinogen temporarily appeared in the urine But though the pruritus disappeared there was no permanent improvement, and sometimes there was a little fever There was no longer any fluid in the general peritoneal cavity, and to account for the distension of the abdomen, it occurred to me that the lesser cavity of the peritoneum might have become shut off for some unknown reason (for instance by primary hepatic carcinoma arising in a cirrhotic liver) The possibility of the abdominal distension being due to cystic dilatation of the common bile duct was never suggested, and no operation was undertaken In November the patient had one of her attacks of local pain in the upper front of her abdomen The general condition varied till on January 14 1934 there was sudden cardiac failure followed by death

Necropsy

The post mortem examination showed a relatively fine hobnailed liver, and the great distension of the abdomen was found to be due to a cystic dilatation of the common bile duct as large as a man s head if not larger Hæmorrhage from a slit like tear or perforation on the right side of the wall of the cyst was evidently the immediate cause of the fatal collapse both the cavity of the cyst and the peritoneum being filled with a thin icteric fluid mixed with blood and much blood clot

On the deeply jaundiced body there were no petechiæ or ecchymoses There was no clubbing of fingers or toes

The tough somewhat finely hobnailed, greenish liver measured horizontally (breadth) 28 cm and vertically (from base to lower edge) 15 cm It could not be weighed separately as it was desired to preserve the specimen showing the connection of the cyst to the liver and duodenum The upper portion of the duodenum was increased in length apparently owing to its having been stretched over the wall of the cyst The distance of the pylorus from the papilla of Vater was 15½ cm The terminal portion of the common

intelligible when one remembers that there is usually no actual stenosis of the terminal portion of the common bile duct The chief sign was the abdominal swelling which was recorded in 30 cases Fever was mentioned in 16 cases, and emaciation in 8 cases a certain degree of ascites was noted in 2 cases

They recommend choledocho duodenostomy as the operation of choice excepting in those rare cases of cystic diverticulum in which excision of the cyst can be practised Here one may note that in a quite recent paper on Cyst of the Common Bile duct D G Duff[7] whose patient was a woman aged 62 years remarks that the operation of choice is the simple one of a primary anastomosis of cyst to gut except where the cyst is so small and so free from adhesions as to be easily extirpated

In true cases of cystic dilatation of the common bile duct external drainage has not been successful Olivecrona s case was first operated by anastomosing the cyst with the stomach This was followed by fever etc and then anastomosis with the duodenum led to cure[8]

Much information on the subject has been summarized by Sir Humphry Rolleston and Dr J W McNee in their work on Disease of the Liver, and their selected data supplement those collected by Seneque and Tailhefer On the whole it can hardly be doubted that in typical cases the cystic dilatation is developmental and not due to obstruction though papillomatous growths (possibly due to irritation) or calculi have been found in some cases Obstruction is not known ever to have produced such enormous dilatation together with great thickening of the duct wall When complete obstruction does finally occur as it did in the present case it is probably almost always due to pressure of the cyst on the undilated terminal portion of the common bile duct especially the intra mural duodenal segment The plausible analogy with megalocolon congenitum some cases of megalœsophagus (idiopathic dilatation and hypertrophy of the œsophagus) and idiopathic dilatation of ureters (megalureter) should be still entertained In fact I propose to call the condition of cystic dilatation of the common bile duct idiopathic *megalocholedochus* by analogy with idiopathic *megalocolon megalœsophagus* and *megalureter* What causative part if any the sphincter of Oddi plays is doubtful

The hepatic cirrhosis may possibly not have been merely biliary

D G Duff *B t J ur Su g* 1934 **21** 53?
Olivecrona, quoted by Rolleston and McNee (*bel w*)
[8] Rolleston and McN *Diseases of the Li er Gall bladder and Bile-d cts* third edition 19 9 7 0-123

1903,[4] I defined biliary cirrhosis as any cirrhosis of the liver originating from disease of the biliary ducts or obstruction to the outflow of bile The apparent increase of biliary canaliculi I pointed out, was not a necessary feature, and I urged that the history as well as the anatomical features should be taken into consideration in deciding which cases of cirrhosis were to be termed biliary In the present case the evidence is at least in favour of a 'biliary obstructive factor in the causation

Remarks

J Seneque and A Tailhefer[5] in 1929 described a case of cystic dilatation of the common bile duct (congenital dilatation of the choledochus) in a woman, aged 32 years which was cured by the operation of choledocho duodenostomy Incidentally, they mention that a fragment removed from the wall of the dilated duct showed it to be fibrous (as in the above case) without any epithelial lining A similar finding has been mentioned by others

Seneque and Tailhefer made a careful analysis of 82 cases from the literature of the subject besides their own (the 83rd case) Of these 83 cases, 60 were in females and 16 in males, whilst in 7 the sex was not mentioned In most cases the age at which the symptoms attracted attention was between 10 and 30 years The terminal (duodenal) portion of the common bile duct is nearly always (as in the present case) not involved in the dilatation but may be closed by pressure from the dilated portion of the duct The cyst like dilatation may be enormous (as in the present case) and the hepatic ducts are occasionally involved in the dilatation (as the cystic duct was conspicuously in the present case) In a few cases there was only what may be termed a cystic diverticulum of the common bile duct In certain cases such as that of a girl aged 6 years described by W G Wyllie [6] the liver was cirrhosed

In regard to clinical diagnosis they note that painful crises something like hepatic colic occurred in 37 of the 83 cases Jaundice was a feature in 52 of the cases The degree varied greatly and just as the pain the jaundice might be intermittent This is very

[4] F P Weber *Trans Path Soc Lond* 1903 **54** 103

[5] J Senèque and A Tailhefer *Jour de Chirurg* Paris 1929 **33** 154–178 Mr David Greig has kindly drawn my attention to a quite recent paper by A Tailhefer in which he described another case (*Bull et Mém de la Soc nat de Chirurg* Paris 1934 **60** 8) His patient was a woman aged 23 years and he performed a successful choledocho duodenostomy Yet another case in a woman aged 24 years in which the same operation was fatal was described in the same paper with Tailhefer's

[6] W G Wyllie *Lancet* 192[illegible] **1** 1342

reconcilable with the lesions of the inter muscular nervous plexus reported by A F Hurst and others in certain cases of megalœso phagus (achalasia of the cardia), and with various alleged causes of that condition arising in adults

It would likewise serve to explain the cases of megalocolon apparently supervening in adult life In this connexion a recent paper by H Burrows (*Brit Journ Surg*, 1934 **21**, 577) is very interesting for he found that in rats enlargement of the cæcum could be brought about by injections of crystalline silica into the mesentery of the cæcum Burrows points out that the modern operation of ramisectomy and sympathectomy, as introduced by R B Wade and N D Royle (*Med Journ Australia*, 1917, **1**, 137) for the cure of megalocolon (or as it is usually termed mega colon), puts the responsible over active sympathetic nerves out of action leaving the parasympathetic system intact Powdered crystalline silica he suggests might act by causing chronic irritation of the local sympathetic nerves

As to the causation of the hepatic cirrhosis in my case I pointed out that the evidence was at least in favour of the cirrhosis being biliary although it was not strictly unilobular (monobular) in type The cirrhosis however did not appear to be merely due to obstructive dilatation of the intra hepatic biliary ducts that is to say it did not seem to be entirely due to distension of the biliary passages analogous to that of the urinary passages which causes the renal changes in cases of hydronephrosis By analogy with hydro nephrosis V S Counseller and A H M McIndoe (*Surg Gyn and Obst* 1926 **43** 729) aptly introduced the term hydrohepatosis for the alteration in the liver due to prolonged obstructive distension of the intra hepatic biliary passages

In regard to recent literature *see* especially R E Gross *Journ Pediat* 1933 **3** 730, F H Hutchins and G B Mansdorfer, *Journ Amer Med Assoc* 1944 **125** 202 Sir J Walton *Brit Journ Surg*, 1939 **27** 295 S T Irwin and J E Morison *ibid*, 1944 **32**, 319

(*see* above remarks), as it has been suggested to have been in Wyllie's and some other cases *The possibility of the abdominal swelling* being due to hydatid ovarian or pancreatic cyst need hardly be mentioned in connexion with the present case In regard to *diagnosis* a great point, apart from exploratory laparotomy, is to remember that the occurrence of cystic dilatation of the common bile duct is not so rare as to be negligible Had the bare possibility of its being the cause of the clinical symptom complex been thought of the diagnosis would certainly have been arrived at in the present case for practically no other condition could have accounted for the great abdominal distension, in addition to the intermittent or remittent jaundice the recurrent attacks of upper abdominal pain and the evidence of hepatic cirrhosis The cyst like enormously dilated choledochus in my case had a thickened *hard* wall at the post mortem examination, and this should be remembered when examining doubtful cases clinically—the hardness of the mass making it seem as if it could not be cystic The early age of the patient and her sex should have added weight to the almost overwhelming points in favour of the correct diagnosis

Addendum (February, 1946)

In the above paper I wrote that I thought that the plausible analogy (referred to by Rolleston and McNee) between cystic dilatation of the common bile duct megalocolon some cases of megaloesophagus (idiopathic dilatation and hypertrophy of the oesophagus), and idiopathic dilatation of ureters should be still entertained Indeed the superficial analogy between all these so-called idiopathic conditions is so decided that whatever their real exact ætiology may be, cystic dilatation of the common bile duct[10] can well be termed *megalocholedochus to bring it into line with* megalocolon megalœsophagus and megalureter At least some cases of these various conditions must be of congenital developmental origin and due as Mr D M Greig puts it to a localized autonomic neurodysplasia There is no reason, however why some cases at least of megalocolon and megalœsophagus should not be acquired, and due to injury of the autonomic nervous supply from inflammatory or other acquired lesions This idea would be

[10] It is to be noted however that the dilated portion of the wall seems to be entirely fibrous and that in some cases the cystic dilatation appears not to involve the whole wall but to be of the nature of a diverticulum from a portion of the wall as pointed out by H W S Wright and others

very feeble Skiagraphic examination of the thorax showed that the spherical shadows in the lungs had somewhat increased before his death on October 8 1934

At the *necropsy* the man was shown to have a malignant renal tumour with pulmonary metastases the urinary bladder was seen to contain four fibrinous balls The largest of these was of the shape and size of a hen s egg about 5 cm and 4 cm respectively in its longest and shortest diameters When an incision was made into it, it was found to consist of concentric fibrinous layers, separating easily like the leaves of a boiled Spanish onion This (the largest) one was not hollow but each of the other three had a central cavity Of these, one was found broken at necropsy and one had a reddish fibrinous cord 15 cm in length attached to it, evidently a string like blood clot from the right ureter as subsequent examination showed To the broken ball also a small thread like thrombus about 2 cm long was attached

The much enlarged right kidney contained a neoplasm some of which had undergone necrosis and cystic formation The pelvis of this kidney was filled with a projecting portion of the new growth with a little clot adherent to it from which apparently the long string like blood clot above mentioned had become separated The right suprarenal gland was stretched out over the right kidney

The left kidney contained one small tumour nodule and showed slight chronic interstitial nephritis The left suprarenal gland was normal There was slight diffuse enlargement of the prostate The bladder was somewhat dilated but neither hypertrophied nor fasciculated and there were no diverticula its mucous membrane was smooth and normal There were several metastatic tumours of various sizes in the lungs but otherwise nothing special was found *post mortem* The central nervous system was not examined Microscopical sections were made of part of the large tumour in the right kidney of the little tumour in the left kidney and two of the lung tumours All show typical clear celled primary carcinoma of the kidney (so called hypernephroma or Grawitz tumour)

The specimens are now in the Museum of the Royal College of Surgeons of England The largest of the four fibrinous balls from the bladder had been incised and shows well the onion like fibrinous laminæ of which it consists Another ball was hollow and had a long string like fibrinous cord attached There can hardly be a doubt that the membrane like material some of it of cystic aspect which the patient passed with his urine on September 20 1933

XIX

FIBRINOUS MEMBRANE-LIKE MATERIAL PASSED IN THE URINE

Large concentrically laminated fibrinous balls in the urinary bladder at the necropsy[1]

THE patient A Y , then aged 64 years, was first admitted to hospital on September 20 1933 On the morning of that day he had twice tried in vain to pass urine but then on trying for the third time a considerable amount of unorganized, nearly homogeneous membrane like material came away He brought it with him to hospital and it was ultimately shown to be fibrinous The urine brought with the fibrinous material was not macroscopically coloured with blood but microscopically it contained erythrocytes and some leucocytes Next day the urine contained a little albumen In hospital, the patient who had been previously complaining of dyspeptic symptoms was feeble and anæmic and suffered from diarrhœa and fever, from which he recovered in October (1933) In November he was still anæmic (hæmoglobin 50 per cent) and the differential leucocyte count showed a moderate eosinophilia of 6 per cent on other occasions there had been no excess of eosinophils Skiagrams of the thorax both antero posterior and lateral showed several spherical bodies of various sizes in the lungs As these seemed not to be increasing very rapidly in size the question of their being hydatid cysts was considered but intradermic antigenic reactions after Dr N Hamilton Fairley were completely negative A cystoscopic examination (Mr A Compton) showed nothing abnormal the fibrinous material had apparently been all passed

In December a little clot was passed in the urine and again later In May 1934 the urine contained albumen (3 per mille Esbach) and a few erythrocytes leucocytes and granular tube casts

The shadows in the lungs were supposed to represent metastases from some primary malignant tumour the position of which could not be determined For a time the patient had been subject to severe pain in the right loin especially at night but the tumour in the right kidney was not detected On October 2 a few days before death the urine contained 4 per mille albumen (Esbach), with some erythrocytes leucocytes and granular casts

The patient s general condition slowly worsened and he became

[1] After *Trans Clin Soc Lond* 1934 **57** 123 and *Journ Path and Bact* 1935 **40** 351

always present and towards the end of his life as much as 3 or 4 per mille of albumen (Esbach) perhaps partly due to the presence of blood plasma

Loose fibrinous balls are occasionally found in the serous cavities especially the peritoneum and sometimes in hydroceles At the clinico pathological meeting of the Section of Urology Royal Society of Medicine, on January 26, 1928 Mr A Clifford Morson (*Proc Roy Soc Med* 1927 28 21 909) exhibited a ball about three times as large as a hen s egg which had been removed *post mortem* from the peritoneal cavity of a uræmic old man It consisted of concentric fibrinous laminæ deposited over a central core possibly a cast off calcified appendix epiploica Mr C A R Nitch showed a laminated fibrinous ball which had been deposited round a metal nucleus of some kind in the perivesical tissue (*Proc Roy Soc Med*, 1927 28 21 1890) In the Museum of the Royal College of Surgeons (no 6133 1) is a much larger fibrinous ball deposited over a separated fragment of omentum It was found in the peritoneal cavity of a whale Apparently of similar nature, though not quite unattached were some pedunculated pea like globular nodules which I once saw at a necropsy attached to the edges of the lower surfaces of the lung in an elderly woman In a similar way arise some of the free rice grain bodies in joints and synovial cavities At a meeting of the Section of Surgery of the Royal Society of Medicine on December 5, 1934 Mr Duncan Fitzwilliams showed several free large smooth olive shaped bodies of this nature which he had removed from an enlarged bursa Little polypoid growths from the wall had evidently become strangulated and had dropped off to become free bodies and ultimately to be covered with concentric layers of fibrin

When fibrin is deposited on surfaces which have not been cut off from the general circulation of blood the fibrin is likely to become organized and to give place to fibrous tissue Thus fibrinous deposits in the pleuræ may become organized and give place to fibrous thickened pleura and in a similar way fibrinous deposits on the surface of the liver may develop into the condition known as Zuckerguss Leber

over a year before his death, was of similar nature to the fibrinous balls found in the urinary bladder Evidently in September, 1933 he succeeded in completely freeing his bladder of its fibrinous content which accounts for its being empty when the cystoscopic examination was made afterwards

Fibrin Balls in the Urinary Bladder

The chief pathological interest in the case here described seems to me to be connected with the presence of the free (unattached) fibrin balls in the urinary bladder *This feature must be one of* extreme rarity I only know of two other comparable cases

1 In the recent case of a woman aged 34 under the care of my colleague Dr E Schwarz, with a Grawitz tumour of the right kidney, necropsy showed an old fibrinous clot curiously shaped like an *Ascaris lumbricoides* in the right ureter

2 Professor A E Boycott, who kindly examined the specimen from Dr Schwarz s case, mentioned to me that Professor M J Stewart had once found in the urinary bladder at a *post mortem* examination a number of concentric laminated unattached fibrinous balls up to an inch or more in diameter Professor Stewart informs me that on opening the urinary bladder he thought he had lighted on a nest of hydatid daughter cysts They were very soft quite spherical and perfectly smooth on the surface They were apparently composed of laminated fibrin

The condition might obviously be compared to the occasional occurrence of unattached ball thrombi of considerable size in the cavities of the heart generally the left auricle in cases of mitral stenosis and which are sometimes multiple (compare with the original description by William Wood *Edinburgh Med and Surg Journ*, 1814 **10** 50) Here the fibrin is supposed to be deposited in layers from the moving blood and the interior may undergo a kind of autolytic softening Originally of course there must have been a central nucleus of some kind probably a piece of vegetation which subsequently became detached with the globular thrombus covering it

In the case here reported the fibrin was apparently deposited from the urine perhaps around portions of thrombus from the right ureter arising in the first instance in relation to the renal neoplasm It is noteworthy that although the patient s urine hardly ever contained macroscopically visible blood microscopically traces were

always present and towards the end of his life as much as 3 or 4 per mille of albumen (Esbach), perhaps partly due to the presence of blood plasma

Loose fibrinous balls are occasionally found in the serous cavities, especially the peritoneum and sometimes in hydroceles At the clinico pathological meeting of the Section of Urology Royal Society of Medicine, on January 26 1928 Mr A Clifford Morson (*Proc Roy Soc Med*, 1927 28 21 909) exhibited a ball about three times as large as a hen s egg which had been removed *post mortem* from the peritoneal cavity of a uræmic old man It consisted of concentric fibrinous laminæ deposited over a central core, possibly a cast off calcified appendix epiploica Mr C A R Nitch showed a laminated fibrinous ball which had been deposited round a metal nucleus of some kind in the perivesical tissue (*Proc Roy Soc Med*, 1927 28 21 1890) In the Museum of the Royal College of Surgeons (no 6133 1) is a much larger fibrinous ball deposited over a separated fragment of omentum It was found in the peritoneal cavity of a whale Apparently of similar nature though not quite unattached were some pedunculated pea like globular nodules which I once saw at a necropsy attached to the edges of the lower surfaces of the lung in an elderly woman In a similar way arise some of the free rice grain bodies in joints and synovial cavities At a meeting of the Section of Surgery of the Royal Society of Medicine on December 5 1934 Mr Duncan Fitzwilliams showed several free, large smooth olive shaped bodies of this nature which he had removed from an enlarged bursa Little polypoid growths from the wall had evidently become strangulated and had dropped off to become free bodies and ultimately to be covered with concentric layers of fibrin

When fibrin is deposited on surfaces which have not been cut off from the general circulation of blood the fibrin is likely to become organized and to give place to fibrous tissue Thus fibrinous deposits in the pleuræ may become organized and give place to fibrous thickened pleura and in a similar way fibrinous deposits on the surface of the liver may develop into the condition known as Zuckerguss Leber

XX

ACROPARÆSTHESIA WITH HEBERDEN'S NODES[1]

ACROPARÆSTHESIA may be symptomatic of Definite neuritis (toxic or infective), a metabolic disturbance of pregnancy pernicious anæmia (as an early sign of combined degeneration of the spinal cord) early tabes dorsalis, disseminated sclerosis, or spinal gliosis early Raynaud s *disease and sclerodactylia, acromegaly Paget s* osteitis deformans, cervical ribs and so called scalenus syndromes Dr L Rau has met with it in association with Hyperostosis frontalis interna (the Morgagni Stewart Morel syndrome) and likewise in a (proved) case of periarteritis nodosa It may occur in the 'Bornholm disease Most cases are, however, so called idiopathic ones and of relatively mild degree

'Idiopathic acroparæsthesia in the above sense is the term applied to sensations like numbness and pins and needles generally limited to the extremities especially the fingers often worst in winter and the early morning Women are more affected than men A large proportion occur in women of climacteric or post climacteric age *in association with Heberden s nodes* and such cases before the world war of 1914 1918 were sometimes termed (e g , by Oppenheim and Cassirer) acroparæsthesia of the Rosenbach type from a paper by Rosenbach (*Centralbl f Nervenheilk* 1890 13 199) two years before Schulze (*Deut Zeitschr f Nervenheilk* 1892 3 300) first introduced the term acroparæsthesia

Heberden s nodes are constituted by osteoarthritic bony enlarge *ment (mostly twin tubercles) at the dorsal base of the terminal* phalanges When they commence to develop they may be somewhat tender and the skin over them may be slightly reddened but after wards they are not associated with redness or local tenderness and must of course be distinguished from the (now relatively rare) tophaceous swellings of chronic gout in the same situation

Though Heberden s nodes may be met with in elderly women who have never done any hard work with their hands (constitutional predisposition may undoubtedly play a part) they are far more often seen in those who have had to do manual housework more or less like a charwoman —and in those who have done much needle work or knitting That is why I think they have been very frequent during the recent war amongst women who previously had been unaccustomed to hard work of any kind

[1]After *Med Press and Circ* 1945 214 2 6

Ordinary (idiopathic) acroparæsthesia is undoubtedly often brought on or favoured by having to keep the hands much in water for instance in washing clothes or washing up after meals The frequent association of the two troubles namely, acroparæsthesia and Heberden s nodes as noted, for instance in hospital out patient work during the recent war—so as almost to constitute a syndrome —is therefore very intelligible Much still remains however to be elucidated in regard to both troubles

Acroparæsthesia[1]

In a letter to *Brit Med Journ* (1945 2 701) I wrote

Dr F M R Walshe (*Brit Med Journ* 1945 2 596) elaborates a simple explanation for the majority of cases of acro paræsthesia in women From his array of circumstantial evidence he suggests that most cases constitute a rib pressure syndrome due to atonic drooping of the shoulder girdle the rib in question being the normal first rib The word atonic in this sense should I think refer not merely to muscle but also to ligamentous and other fibrous constituents of the shoulder girdle

I have been more or less interested in acroparæsthesia almost since the term was first introduced fifty three years ago (Schulze *Dtsch Z Nervenheilk* 1892 3 300) but the increased number of cases during the war (notably in hospital out patients) made me recently sum up the main data bearing on the nature of the con dition (Weber *Med Pr* 1945 214 226) as I saw them and I re marked that much still remained to be elucidated Dr Walshe s paper does I think really throw some fresh light on the subject and he comes to a conclusion of fair plausibility With Ben Jonson one may say

How near to good is what is fair
Which we no sooner see
Than with its form and outward air
Our senses taken be

There is however one feature which Dr Walshe does not take into consideration—namely the frequency of the association of acroparæsthesia in middle aged women with Heberden s nodes This has been obvious during the recent war but the frequency of this association was already observed by Rosenbach (*Z Nervenheilk*

[1] *B t Med J urn* 1945 2 701

1890 13, 199) two years before the actual term acroparæsthesia' was first introduced Indeed, Rosenbach, from a study of cases of acroparæsthesia, seems actually to have re discovered and carefully re described what we usually call Heberden's nodes To a certain extent this association supports Dr Walshe s explanation In my recent account (cited above) I wrote

Though Heberden s nodes may be met with in elderly women who have never done any hard work with their hands (constitu tional predisposition may undoubtedly play a part), they are far more often seen in those who have had to do manual housework more or less like a charwoman—and in those who have done much needlework or knitting That is why, I think, they (Heberden s nodes) have been very frequent during the recent war amongst women who previously had been unaccustomed to hard work of any kind

Heberden s nodes, as I understand them constitute a conservative *osteo arthritic reaction* towards stress of work involving the finger tips When they commence to develop there may be slight local tender ness and redness of a mild *non infective inflammatory* (i e *reactive*) nature, but afterwards when once fully developed they are not tender and the skin is not red over them and they give rise to no trouble except from their unsightliness I take it that Heberden s nodes represent a conservative reaction occurring especially in middle aged or elderly women of an osteo arthritic disposition as a result of too frequent (though usually mild) traumatic stress which in many other individuals would not be sufficient to call forth any similar reaction In other words, Heberden s nodes are the expres sion of a reaction towards stress of work comparable to the stress of work which calls forth the ordinary rather mild complaint known as acroparæsthesia Contributory predisposing factors in both complaints probably include nutritional and general hygienic errors, climacteric changes and over fatigue These considerations, as far as they go, support Dr Walshe s main conclusions

Postscript —Compare also J Purdon Martin Acroparæsthesia in the Lower Limbs *Brit Med Journ* 1946 1 307

XXI

FAMILIAL ASTHENIC ('PARALYTIC') TYPE OF THORAX

With Congenital Ectopia of Lenses

A Condition Allied to Arachnodactylia[1]

ARACHNODACTYLIA (spider like fingers) is a mutational abnormality of development which has been sometimes thought to be aetiologically connected with a defect in the pituitary gland, or some other endocrine disturbance Typical examples are characterized by thin limbs with long tapering fingers and toes an asthenic ('paralytic') type of thorax poor development of skeletal muscles and ectopia of lenses with iridodonesis (trembling of the iris on movements) Some of the following defects—all doubtless congenital developmental or on a congenital developmental basis—may be associated slight scoliosis kypho scoliosis kyphosis or lordosis loose joints over extensibility of fingers genu recurvatum slight contraction of muscles of arms scaphoid scapulae high arched palate slight abnormality in shape of external ears slight webbing of fingers slight congenital cardiac malformation cyclic vomiting slight acrocyanosis The intelligence is generally quite up to the average

A few years ago R W B Ellis demonstrated a girl aged 8 years who showed some features of arachnodactylia (with ectopia of lenses) and also had fragilitas ossium with blue sclerotics (what some French authors call Lobstein s disease after the author of the *Traité d Anatomie Pathologique* published in 1833) the blue sclerotics being apparently inherited through the mother the arachnodactylia through the father

There are doubtless congenital developmental conditions allied to arachnodactylia in some of which the spider finger feature may be absent—that is to say the fingers and toes though rather thin and long may yet be within extreme normal limits in length For such cases the term dolicho stenomelia (long slender limbs) introduced by Marfan of Paris in 1896 is more truly descriptive than the term arachnodactylia suggested in 1902 by Achard of Paris and now generally employed In some cases the limb features may be more characteristic in upper than in lower limbs

[1] *Lancet* 1933 2 1472

Proc Roy Soc Med 1931 24 54 (Sect Dis Child) Case 3

In illustration I will now give a short account of a brother and sister whom I have lately seen with an asthenic habit of body—especially a 'paralytic' type of thorax—and congenital ectopia of lenses

The *brother*, aged 19 years, is a somewhat lanky pigeon chested scoliotic youth, with a few 'striæ atrophicæ' of the skin over his shoulders and groins, such as occasionally occur in connexion with rapid growth about the period of puberty without any other obvious causation [1] Shortly after a long fatiguing day's walk in 1930 he became severely ill with what seems to have been venous thrombosis in the left thigh, and about a year later (1931) he had a similar attack in the right lower limb, but less severe and of shorter duration

He has irregular mottled patchy erythema with branched thread like fine telangiectases over both feet more on the left than the right foot and more on the sides than on the back or sole The red patches sometimes become livid, and some of them are very slightly raised The feet are illustrated in the *Proc Roy Soc Med* 1933 1934 27 137 There is no oscillometric or other evidence of any disturbance of the circulation due to obstructive arterial ischæmia, and pulsation is good in the dorsal artery of either foot The patient has however, large dilated superficial veins over the front of the thorax and abdomen apparently connected with compensatory collateral venous circulation and suggesting that there has been venous thrombosis in the iliac veins or even in the lower part of the vena cava inferior In this regard it should be noted that the erythematous telangiectatic condition of the left foot developed shortly after the venous thrombosis in the left lower limb in 1930 and the similar condition in the right foot was first noticed shortly after the venous thrombosis in the right lower limb in 1931

There is aphakia (absence of crystalline lens) in both eyes He had congenital ectopia of lenses and operations had to be performed in 1931 and 1932 on one occasion by Mr Frank Juler (as the latter kindly informs me) owing to acute glaucoma associated with dislocation of the lens forwards into the anterior chamber

The patient's height is 166 cm (without shoes) and his weight is 62 5 kg He is of characteristic asthenic build with long limbs but without the long spider fingers of typical arachnodactylia His legs have apparently become thicker since the attacks of deep venous

[1] Compare F P Weber Causation of Striæ Atrophicæ Cutis Not Due to Stretching of the Skin *Brit Med Journ* 19 8 I 255

thrombosis Röntgen ray examination shows no disease of the thoracic viscera Brachial blood pressure 126/65 mm Hg The blood serum gives negative Wassermann and Meinicke reactions By radiographic examination the pituitary fossa appears normal in size and shape

I am inclined to think that there is an indirect causal relationship between this boy s congenital developmental abnormality of build (allied to arachnodactylia) and the venous thrombosis and the telangiectatic condition of the feet It should be mentioned that slight acrocyanosis has been already noticed in connexion with arachnodactylia

The patient s youngest *sister* aged 15 years (whose eyes my colleague, Dr C Markus kindly examined with me) has extreme myopia iridodonesis (trembling irides) and ectopia (congenital subluxation outwards) of the lens in both eyes She also has slight spinal scoliosis and lordosis and a deep depression or well in the lower part of her chest somewhat resembling funnel chest (*Trichter brust*) her fingers and toes are long but (like her brother s) not longer than the extreme normal limit

The parents both appear to be of normal build fairly thick set and of medium size with fingers rather on the short side of the normal average There is no consanguinity between them and they do not know of any similar abnormalities in their families They have had 14 children of whom the two youngest are the brother and sister with the above described abnormality of build Six others are said to be living and normal The remaining six died of various diseases

Whether or not in spite of the absence of parental consanguinity the above described condition is a Mendelian recessive I regard it as one of the innumerable varieties of congenital developmental mutational abnormalities These can be reduced in frequency by the observance of eugenical considerations but obviously cannot be altogether got rid of for they may always arise *de novo* The number of mutational diseases (and abnormal variations) which have already been described is enormous but many that have been observed have not yet been recorded new ones will arise from time to time and finally atlases and indexes will be required for their proper classification

XXII

PAGET'S BONE DISEASE IN THREE SISTERS[1]

The exact nature and ætiology of osteitis deformans (Paget's bone disease) are still unknown The disease is certainly not of syphilitic origin, as was maintained by Lannelongue (1903) and some other French writers though in rare cases of inherited syphilis in children it may be superficially imitated in a very striking manner, as one of us (F P W, 1908), amongst others, has pointed out

That at least the liability to the disease may be inherited is illustrated by the family under our present consideration, in which three sisters commenced to suffer from typical osteitis deformans in the second half of their lives whilst their nine brothers are said not to have been affected S Maynard Smith (1905) recorded the case of a man, aged 42 years, who had Paget's disease of three years duration and whose father aged 74 years had had Paget's disease for thirty five years The disease therefore commenced both in the father and the son at about 39 years of age A Chauffard (1894) mentioned a woman aged 80 years and her daughter, aged 60 years, both of whom suffered from typical Paget's disease and were likewise somewhat mentally unsound Berger (1903) spoke of an old lady with typical Paget's disease, whose son aged 35 years had Paget's disease of the tibiæ of some years duration Dr E A Cockayne told us that he was recently shown a woman with severe osteitis deformans, whose father, according to the patient's description had obviously suffered from the same disease Dr Cockayne says he is sure there have been reports published of two sibs suffering from Paget's disease and he thinks that mere coincidence can hardly account for the family under consideration with three sisters suffering from so uncommon a disease In fact either Paget's disease itself or some special liability to it must be inherited

The Present Family

A married woman aged 66 years was admitted to hospital in March, 1937 saying that for the last four months or so she had noticed a gradually increasing enlargement of the upper part of her skull more marked on the left side The patient had enjoyed good health and did not actually feel ill Radiographs of the skull showed the changes typical of Paget's disease On further examination of the patient nothing else abnormal was found excepting a

[1] From a paper with Dr H Rast *Brit Med J* 1937 1 918

radiographic appearance of the ischial bones suggesting slight osteitis deformans there also Blood serum gave negative Wassermann and both Meinicke reactions Blood serum calcium 10 4 mg per cent

The patient s eldest sister, born about 1860 is living and healthy according to the patient, excepting that for the last eleven years her shins have been thickened and bent In August 1927 this sister was an out patient at the German Hospital under Dr F J Jauch and radiographs of her skull and right tibia were taken The radiologist Dr E J H Roth reported that the skull and the right tibia showed changes characteristic of Paget s disease

The patient s only other sister who was born about 1867 and died about 1909 had very decided enlargement of the upper part of her skull for the last few years of her life

These sisters had nine brothers, none of whom are known to have been affected with Paget s disease

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Weber F P (1908) *Brit Journ Ch ld Dis* **5** 83

Postscript (1946) —In regard to the supervention of osteogenic sarcoma in Paget s disease, compare T B Davie and W E Cooke *Brit Journ Surg* 1937, 25 299 316 In regard to differential diagnosis it must never be forgotten that osteitis deformans may be monosteotic (e g involving only a femur a tibia or a clavicle) at all events in the early stages also that in many cases by skiagraphic examination the characteristic osteosclerotic appearances may be accompanied by osteoporotic and fibrous appearances (*symptomatic* osteitis fibrosa) elsewhere —F P W

XXIII

THROMBO-ANGIITIS OBLITERANS IN FATHER AND SON[1]

CONSIDERING the fact that in the ætiology of thrombo angiitis obliterans (Buerger s disease) the assumption of some predisposing *constitutional factor is almost necessary*, it is surprising that more than one member of the same family is so seldom affected I mean that the suggested exciting causes such as tobacco smoking do not seem to act in the absence of some unknown constitutional pre disposing factor—possibly a developmental defect in certain blood vessels Moreover I still maintain that, in London at any rate, the majority of the sufferers are members of Central European Hebrew families

Meszaros in 1931 found that eight members of a pure Hungarian family were affected with an arterial disease, but as four of the eight were females and as no microscopic examination was made, I do not think that his cases were true examples of Buerger s thrombo angiitis obliterans as he maintained For the same reason one cannot accept certain cases quoted by Meszaros from other articles on the subject—namely Niemeyer s cases in mother and son and Higier s cases in two sisters—though he also mentions Goldflam s cases in two brothers and Idelson s cases in father and son

Samuels (1932) however wrote —

In the examination of over 500 cases of thrombo angiitis obli terans I have observed three families in which it occurred in brothers In none of these families has there been any history of the disease in parents or grandparents on the maternal or paternal side nor has there been evidence of the disease in other blood relatives

In two of the families three and in the other family two brothers were affected, but in each of the 8 cases heavy cigarette smoking could be adduced as a possible toxic (exciting) cause of the disease

Case Report

In the following cases of father and son now under my observa tion, tobacco cannot be altogether excluded as a cause

The father now aged 58½ a Hebrew cabinet maker from Russia had the small toe *of his left foot amputated in London for gangrene* sixteen years ago Next year (August 1922) his left foot was ampu

[1] *Lancet* 193, 2 72

tated in Berlin The wound did not heal and in the following month his left leg was amputated After this he had no trouble in the stump of his left leg but in 1924 he began to suffer from pains in his right toes In December 1926 he was admitted under my care at the German Hospital London The tip of the second toe of the right foot was black and there was some discoloration of the third and great toes No pulsation was felt in the dorsal and other arteries of the right foot There was normal pulsation in both radial arteries at the wrist Brachial blood pressure 145/80 mm Hg Blood Wassermann reaction negative By ordinary clinical examination nothing else abnormal was found The treatment included intra venous sodium citrate injections, small doses of potassium iodide by the mouth locally hot air baths Bier's passive congestion treatment and the application of xeroform powder Progress was very slow and tiresome partly in hospital and partly in his own home but the tip of the second toe came away spontaneously, and finally healing was complete by the end of 1928 After that he remained well I saw him in April 1937 He says he can walk as much as a mile without stopping though he occasionally feels a little pain in front of the ankle (his only leg) The cure in this case is a functional one there is no pulsation to be felt in the dorsal or other arteries of the foot and the needle of Pachon's oscillometer gives hardly any oscillation with the band round the calf He still smokes about ten small cigarettes daily

The son aged 33 is now in hospital under my care for thrombo angiitis obliterans he was the second son Two years ago he began to have intermittent claudication in the right leg with the usual pain in the calf on walking and since September 1936 he has suffered from ischæmic troubles in the right foot—in spite of intra muscular injections of Padutin and Carnacton He has an ischæmic ulcer on the dorsum of the right foot and the black mummified little toe of that foot has just been shed spontaneously He says he has smoked only about ten cigarettes daily Though the left foot appears normal no pulsation can be felt in the dorsal artery of either foot The oscillometer index at calf level is 0 15 on right side 0 3 on left side over the right thigh it is 3 5 and over the left thigh also 3 5 No arterial calcification is seen by radiography in either leg Blood pressure in right arm 140/70 mm Hg in left arm 120/60 mm Hg Blood Wassermann reaction negative Nothing abnormal found in ordinary examination of thorax abdomen nervous re actions retinæ urine and blood (except slight anæmia and leuco

cytosis) Blood sedimentation within normal limits Blood serum cholesterol 150 mg per 100 c cm Blood uric acid 3 mg per 100 c cm *Blood serum calcium 8 4 mg per 100 c cm Fasting blood* sugar 0 113 per cent

There is now hardly any pain and under rest and local applications *the foot is tending to heal A liver extract by the mouth may* be acting favourably

I have never met with thrombo angiitis obliterans in brothers *and only once in father and son—namely in the above* described cases Recently a son of one of my earlier patients returned from America with what he thought might be his father s disease, thrombo angiitis obliterans, but on examination it turned out to be a form of chronic rheumatoid arthritis

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Postscript (1946) —In a paper with Dr H Huber (*Deut med Wochenschr*, 1939 65, 256) further details of the family history of these patients are given In 1944 I was able to examine two Jewish brothers, *aged 35 and 31 years respectively both suffering* from mild but definite signs of thrombo angiitis obliterans of lower limb

XXIV

AGNOSIA OF HEMIPLEGIA AND OF BLINDNESS AFTER CEREBRAL EMBOLISM[1]

A WELL BUILT man aged 52 came under my observation in November 1939 with signs of subacute or chronic bacterial endocarditis (endocarditis lenta), which was probably already of about a year s duration On March 16, 1939 he had had a severe cerebral stroke with coma and right hemiplegia lasting a few days but with aphasia alexia and agraphia of much longer duration In fact in November though the hemiplegia had cleared up he still had a trace of aphasia and was diligently learning to read and write again On August 1 1940 he had another and severer attack of coma this time with left hemiplegia—evidently due to right sided cerebral embolism just as the previous attack had been due to left sided cerebral embolism In the course of many days he slowly recovered from the coma but the paralysis of the left limbs persisted together with the complete blindness of cortical type which accompanied it He could not get about and lay in bed with his eyes and head directed to the right and was unaware of his blindness and of his hemiplegia both of which he denied However after this last terrible stroke there was no sign of active bacterial endocarditis though of course the loud mitral systolic murmur persisted The last positive blood culture for a *Streptococcus viridans* was on April 12 1940 I have already described the case as far as the bacterial endocarditis was concerned (Weber 1941) I shall deal here only with the neurological aspect of the case

From February to April 1941 he remained helpless lying in bed with conjugate deviation of the eyes and head to the right—that is towards the side of the more recent and more extensive cerebral damage Complete spastic paralysis of the left upper and lower extremities Very slight left facial paresis of cerebral type Pupils large and equal reacting slightly to light He was completely blind in both eyes though repeated ophthalmoscopic examinations (Dr Charles Markus) showed no changes in the fundi Patellar and Achilles reflexes active more so on the left Plantar reflex of normal flexor type on the right doubtful on the left Superficial abdominal reflexes not obtained

Sensation Perception and Intelligence —He had complete anæsthesia of his left (paralysed) limbs excepting that a tactile or painful

[1]Somewhat enlarged from the *Lancet* 1942 1 44

stimulus to these limbs appeared sometimes to be referred to the *trunk or to the right limbs (allæsthesia) On other parts of his body* he could not always distinguish the position of a tactile stimulus (allachæsthesia), for instance he confused stimuli on his ear, nose and hairy scalp With his right hand (the left one was as stated quite anæsthetic) he could not in the least distinguish one object from another when holding and feeling it (bunch of keys watch coin book, bottle), but he could detect a gross difference in weight The astereognosia of objects held in his hand made one think of the want of *recognition in cases of mind blindness and mind deafness* On one occasion he said that the sound of a watch was like the sound of running water, but on another occasion he recognized the ticking of a watch when held to either ear He could recognize the sound of metal being struck close to him He could not always distinguish between the voices of those he knew Nor could he always recognize the direction from which sounds came—there was often confusion of laterality In regard to taste and smell he could distinguish eau de Cologne when it was held to his nose and a drop of cognac when placed on his tongue Apparently he could distinguish fairly well the taste of ordinary foods and sweets especially of chocolate, of which he was fond

He was unaware of (did not perceive) his blindness and his hemiplegia and denied them both (anosognosia Anton Redlich Bonvicini syndrome) When asked to give his left hand he invariably gave his right hand When I placed his right hand against his left (paralysed and anæsthetic) hand he did not recognize that it was his left hand till he was told the left hand felt to him like any object which owing to his astereognosia he was unable to distinguish Moreover, he often made mistakes between right and left both in speech, when saying from which direction he thought a sound was coming and in pointing with his right (unparalysed) hand When asked how many fingers and toes he had he seemed to be calculating mentally and answered that he had ten toes but stopped at nine fingers Yet in regard to simple small arithmetical calculations there was no acalculia—he answered quickly that multiplying 8 by 3 makes 24 and similar reckonings were easy to him *In his* business he had been good at figures and al o at distinguishing colour shades but an eye specialist consulted after the first attack of cerebral embolism said that perception of colour had been lost As to his *remembrance* of colour he could not revisualize correctly he told me that his hair was light and that he had blue eyes, whereas in reality

his hair was dark and he had brown eyes On the other hand, he said he preferred blue clothes which according to his wife, he actually used to like In regard to his memory generally, he was right (according to his wife) when he told me there were five rooms in his last home before coming to England Apparently he could not always find the word he wanted but in conversation he could answer questions more readily than ask them, excepting, of course, when he asked for food or other necessaries He talked preferably in German, his native language but probably understood as much English as he had ever known On one occasion he dictated sensible letters to his two children in America, but his condition varied Sometimes there was disorientation in time and place He had periods of restlessness and bodily pains when he made a good deal of noise and sedatives were necessary, at such times especially there was occasional incontinence His appetite was as a rule remarkably good almost a bulimia as if his sense of satiety had been lost The recurrent periods of pain—especially in the lower trunk and thighs more on the left (hemiplegic) side—were I suspect connected with his cerebral damage, and so, probably were the periods of great restlessness He died on April 28 during one of his periods of restlessness at a home to which he had been removed on February 28 Towards the end he lost much weight in spite of continued good appetite

There was no autopsy but his cerebral symptoms must have been due to large destructive lesions on both sides of the brain caused by embolisms from his endocarditis lenta That in the left (dominant) hemisphere probably included part of the optic thalamus and the radiating connexion with the occipital cortex that in the right (minor) hemisphere probably involved the optic thalamus and included the radiations to the occipital and part of the parietal lobe cortex The lesion in the minor hemisphere doubtless gave rise to the remarkable Anton Redlich Bonvicini syndrome—the imperception or agnosia of his blindness and left hemiplegia The cerebral stroke of March 1939 was probably due to embolism of the posterior cerebral artery of the left (dominant) hemisphere while in the attack of August 1940 there was doubtless embolic obstruction in the right posterior cerebral artery but the resulting cerebral necrosis seems to have been more extensive

Discussion

The Anton Redlich Bonvicini Syndrome —Imperception or agnosia of the signs of grave organic cerebral disease—hemiplegia or cerebral

cortical blindness or deafness—has not often been described in England Anton (1889) was the pioneer observer of this class of case He reported 3 cases of imperception of blindness or deafness of cerebral cortical type His views were criticized by Redlich and Bonvicini (1908 and 1911), who described cases of their own Babinski (1923) introduced the term 'anosognosia Barkman (1925) summed up the literature and noted that up to 1925 in every case of agnosia of hemiplegia the hemiplegia had been on the left side—that is to say, it was produced by a lesion of the right (presumably minor) cerebral hemisphere—but Schilder (1935) narrated the case of a woman aged 48, with severe right hemiplegia and imperception of it In that patient the dominant hemisphere was presumably the right one and the left was the minor one

Among striking cases in which the neurological symptoms more or less resembled those in my present case are some recorded by Kramer (1915) Potzl (1924) Von Hagen and Ives (1939), and Nielsen and Sult (1939), in whose fifth case the neurological picture was in many respects identical with that of my present case

Their patient a man aged 52 had developed left hemiplegia suddenly five years previously and complete blindness had followed a cerebral stroke on the day before admission On feeling his left hand with his right he had the illusion that the left belonged to someone else He had agnosia of his left side unless his attention was specially called to it Asked to place his right hand on his left ear he placed it on the right one Asked to place his left hand any where he used his right one Asked how many ears eyes, feet or hands he had he always said one Asked how many fingers or toes he had he counted to ten and then answered twelve He consistently denied his blindness and claimed that he could see everything In broad daylight he thought it was night He could not revisualize correctly He could not recognize objects when placed in his hands He was always hungry (like my patient) Touch or pin prick was more often referred to the other side than to the correct one He was a Mexican and could converse intelligently in Spanish what he had known of English was still familiar to him There was no autopsy, but a *diagnosis of thrombosis of both posterior cerebral* arteries was made

Von Hagen and Ives (1937 and 1939), who have obtained autopsies in some cases of agnosia of left hemiplegia, say that Barkman (1925) thought that involvement of the right optic thalamus was necessary for the production of the anosognosia but from their own

observations they conclude that anosognosia is evidence of a lesion involving the thalamus in the minor hemisphere or situated in the immediate vicinity so as to separate the thalamus from the cortex of the frontal, parietal and temporal lobes

In most typical cases there is also left homonomous hemianopia and tendency to conjugate deviation of the eyes and head to the right, there is also more or less sensory impairment on the left (paralysed) side Schilder (1935), Nielsen and Sult (1939) and others discuss the occasional association of allochiria (allæsthesia) and allachæsthesia in such cases Schilder in discussing a case recorded by Kramer remarks that it is at least probable that the same mechanism which prevents the patient from appreciating his hemiplegia and the left side of his body is also responsible for the transfer of the sensation from one side of the body to the other

It is noteworthy that a cerebral agnosia lesion may cause not only some kind of imperception in an actual limb but also in a phantom limb Thus Schilder quotes from Head

One of our patients had lost his left leg some time before the appearance of the cerebral lesion which destroyed the power of recognizing posture After the amputation as in so many similar cases he experienced movements in a phantom foot and leg But these ceased immediately on the occurrence of the cerebral lesion the stroke which abolished all recognition of posture destroyed at the same time the phantom limb

The Bilateral Blindness of Cerebral Cortical Type —It seems probable that my patient s complete blindness of cerebral cortical type was due to double homonomous hemianopia as suggested to me by Dr Russell Brain The attack of left cerebral embolism in March 1939 probably caused right homonomous hemianopia which was not detected till the right cerebral embolism of August 1940 produced left homonomous hemianopia and thus complete blindness I think that in the fifth case of Nielsen and Sult (1939) to which I have already referred a similar explanation must hold good for the complete blindness which followed the second cerebral stroke, but in their case the left hemiplegia accompanied the first stroke (not the second as it did in my case)

Absolute imperception of visual stimuli (complete cortical blindness) as a result of bilateral damage to the occipital lobes is rare In the remarkable case described by Byrom Bramwell and his colleagues (1915) there was retention of macular as distinct from panoramic vision

A man died of pneumonia at the age of 71, 26½ years after an attack diagnosed as acute nephritis, during which he suddenly lost his eyesight and had a series of epileptiform fits He was unconscious for fourteen days, and it was three weeks before he could recognize voices *When he regained consciousness he was quite blind* but afterwards his central vision was gradually in some degree restored The fundi of the eyes appeared normal, there was neither mind blindness nor word blindness During the remaining twenty six and a half years of his life there were no fresh head symptoms and practically no change in vision no motor paralysis, no loss of sensation, no sensory or motor aphasia A large lesion was found in each occipital lobe at the autopsy

In regard to the retention of *macular vision* Carmichael s case (1930) may also be noted

This was a boy aged 14 in whom Geoffrey Jefferson had performed a right occipital lobectomy After recovery from the operation the patient had left homonomous hemianopia with sparing of the macular region Four months later there was an attack of meningitis and the macular region was found also involved the hemianopic boundary line splitting the macula (passing through the centre of the macular region)

Pain and Hyperæsthesias of Cerebral Origin —Some of the pains so often complained of by my patient were doubtless connected with his cerebral damage and so probably were his periods of restlessness Since anæsthesias and imperceptions of various kinds may certainly be caused by destructive lesions in the brain it seems reasonable *to suppose that hyperæsthesias pain and restlessness* may be due to local irritative lesions or to irritation connected with destructive lesions There are doubtless many other pains of *cerebral origin besides those constituting part of the* thalamic syndrome

Extreme Loss of Perceptions as a Permanent Result of Cerebrla Lesions —Agnosias of various types may *of course be associated with* disorientations and other symptoms in temporary cerebral attacks of ischæmic origin In the following case permanent agnosia for everything resulted *from severe and prolonged biochemical shock,* doubtless associated with very extensive cell necrosis in the brain [2] This most extreme example of sudden loss of perception of sensory

[2] This portion of the paper I have somewhat elaborated in A Note on the Cerebral Causes of Defects in Perception and Consciousness *B t Jou Child D s* 1942 39 15

stimuli was the case of a boy (aged 4 years when I first saw him) which I described (Weber 1931) under the heading 'Complete mindlessness and cerebral diplegia after *status convulsivus* associated with ether anæsthesia A series of convulsions occurring in connexion with an operation under ether anæsthesia at the age of two years had suddenly transformed the hitherto normal child into a decerebrate unconscious automaton He could neither see nor hear nor could he perceive tactile or painful stimuli in the ordinary conscious way Automatic reflex responses could however be obtained When fed with a spoon the food often remained a little time in his mouth, till it was passed on by a reflexly evoked swallowing movement Urine and fæces were passed automatically at intervals Dr W Wilson on examining the child s ears made the interesting observation that nystagmus occurred as in normal individuals on trying the caloric test No palpebral response followed any noise stimulus Though the boy was blind and senseless he sometimes turned his head away from a very strong light All emotional manifestations—smiling laughing crying—were completely absent He was said occasionally to cough, though I never observed that myself The pupils reacted to light The patellar and Achilles reflexes were normal on both sides Superficial abdominal and cremasteric reflexes could not be elicited The plantar reflex in the right foot was of the normal flexor type that in the left foot was different but not definitely extensor in type It almost seemed to me that the nerve cells of the cerebral cortex concerned in voluntary movements and conscious perception of all kinds had been selectively destroyed and I suggested analogy to those cases in which the glandular cells of the whole liver have been more or less selectively destroyed as a result of prolonged chloroform anæsthesia Dr Russell Brain tells me that he has observed a somewhat similar mental and neurological condition in a patient with advanced Schilder s disease To some extent also the condition may be compared to one of lesser degree (about which Dr J G Greenfield told me) in a patient in whom mental imbecility was a permanent result of prolonged hypoglycæmic coma

Amongst other subjects suggested by the present study is the old one of the *simulation of organic cerebral syndrome by various so called functional syndromes* (both paroxysmal and non paroxysmal) in persons with hysterical psycho neuroses Amongst the non paroxysmal static syndromes the hysterical paralyses and anæsthesias and blindness and deafness roughly correspond to the manifestation

of local organic cerebral lesions Hysterical blindness may at first superficially resemble organic blindness of cortical type The turgid redness of the hand supervening in some cases of organic hemiplegia may be roughly simulated by the swollen stiff (but not really paralysed) red or purple hand of psychical origin occurring occasionally in young women This may be interpreted sometimes as a kind of protest —for instance, to avoid unpleasant work or from some other more or less subconscious motive In one such case the localization of the hysterical syndrome was perhaps first suggested by preceding attacks of severe chilblains Such symptoms may persist for months and years if not successfully treated, so that one may really be justified in saying that the condition is due to a *persistent hysterical lesion* in the contralateral cerebral hemisphere though, of course the lesion in question must be supposed to be of so delicate and unstable a nature that it may be both caused and (by successful treatment) removed by emotional and other psychical influences

Summary

In a man of 52 bilateral cerebral embolisms occurred as a result of endocarditis lenta and gave rise to permanent left hemiplegia and complete blindness of cerebral cortical type The patient was unaware and refused to admit the existence of his blindness as well as of his left hemiplegia—the Anton Redlich Bonvicini syndrome This syndrome and subjects suggested by the various neurological features of the case have been shortly discussed

I wish to thank Dr W Russell Brain Dr Charles Markus Dr H K Lauber Dr K Blum and Dr Harry Shaw

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XXV

INFLUENCE OF DR SIGMUND FREUD[1]

I AGREE with Mr Rugg Gunn that it is sometimes right not entirely to hold to the old maxim, *De mortuis nil nisi bonum*, especially in regard to outstanding lights of progress such as the late Sigmund Freud Though at first there is a real danger that something against the hero may be remembered more than his great achievements, such errors are always rectified subsequently when the perspective becomes clearer

Charcot, whom I myself remember, offers a striking example of this By his zealous work and genius for clinical research and teaching he attracted students and doctors from all parts of the world to the Salpetriere in Paris He inspired his internes and visitors with his own spirit His pupils helped him in searching the medical literature of all countries, and he always endeavoured to give credit for every little landmark in neurological progress to the author who had first, or best described a disease a symptom or one of the (now innumerable) syndromes The push that he thus gave to the progress of the study of neurology was almost incredible and yet soon after his death, there were some who thought of him as the physician who had cultivated that specially dramatic type of neurotic attack amongst his female patients known as the *grande hystérie* of the Salpetrière Worse still, everyone knew that Leon Daudet who possessed considerable inside knowledge and had quarrelled with Charcot s son had with too satirical vigour held up the Salpetriere school to ridicule and had even made it appear infamous in Les Morticoles All that has now been rectified and balanced and Charcot s position will remain in medical history unchallenged except by those few who refuse to look up the facts Even with William Osler it was not so long ago that American journalists spoke of him as the physician who (in 1905) advocated a painless death by chloroform for all men soon after reaching 60 years of age

Surely Freud should be remembered chiefly as the man who, in the vast castle of knowledge took the giant s part in helping to break down the barriers leading into the galleries and vaults of the subconscious It is obvious that these galleries and vaults were rather dark, and in the dim light some of the explorers fancied they could see much that was not really there Since then these chambers

[1]Letter *Lancet* 1939 2 906

have been illumined with artificial light and, for the sake of visitors, Freud and especially his English and American followers have adorned the walls with pictures and diagrams illustrating rather dismal subjects, which they had (or thought they had) discovered in some of the deepest of the vaults these subjects extended from the much talked of Œdipus complex to the complicated idea of patricidal anal sadism Inhibitions complexes, obsessions have doubtless been attributed to alleged infantile traumatic experiences in cases in which the latter existed only in the patient s imagination — i e as the result of subjection to the psycho analytical examination—or had really existed but had no causal relation to the present symptoms

I am more sceptical than Mr Rugg Gunn of much permanent harm having been produced by the Freudian psycho analysts, but a few years ago scientific lecturers on the wireless seemed to have accepted some of the more dubious Freudian doctrines as having been founded on genuine scientific deductions I wonder whether they had examined the evidence adduced in writings by London followers of Freud to prove the correctness of many of their psycho analytical diagnoses

I do not see how Freud can be held responsible directly or indirectly for the present prevalence in England of certain *minor* Oriental evils under which I would include dyed finger (and toe) nails artificially altered eyebrows and the abundant use of lipstick and face painting—which latter two often produce an appearance reminding me of an embalmed person I was once shown inhabiting the library of the house that during life he had owned I do not think however that our Phœnician Jezebels should be cast out from an upper window at the approach of Jehus or at the instigation of Puritan prophets but perhaps Englishmen might somewhat less encourage the employment in young women of such artificial supposed improvements and charms

Anyhow it will be on solid ground that Freud s pioneer work will be immortalized in medical and psychological history

XXVI

ARGYRIA AND 'BISMUTHIA'[1]

It seems to me that in cases of pigmentation due to generalized argyria of unknown origin one has nowadays to think of the possibility of prolonged use of gargles, mouth washes, mouth applications, and intra-nasal sprays containing silver, just as thirty or forty years ago one had to think of the possible prolonged use of silver nitrate pills for pains supposed to be due to gastric ulcer. Patients still insist on using old prescriptions whenever they think they are again suffering from the old symptoms. Moreover, I am sure that the majority of doctors do not know that the prolonged use of preparations such as argyrol for the throat, mouth, or nose, can produce generalized argyria. This was evident at last year's annual meeting of the British Association of Dermatology and Syphilis at Manchester.

Amongst many other patients a woman was shown with considerable facial pigmentation, which I thought must almost certainly be due to generalized argyria and not to haemochromatosis. She seemed to be otherwise healthy and knew nothing of any silver medication, but admitted the prolonged use of a gargle or mouth wash. I suggested that this might have contained argyrol. A doctor at the meeting was astonished, and told me he constantly used argyrol for himself and his family for any soreness of the throat, etc. I had, however, not long previously been informed about a doctor in America who did the same thing, with the result that he developed generalized argyria, shown by pigmentation of the face. It turned out afterwards that I was wrong in my suggestion regarding the patient in Manchester, for it was ascertained that the mouth wash or gargle she had been using was made up, not with argyrol, but with simple silver nitrate.

But can one be certain that most cases of leaden or bluish-blackish pigmentation of the face in apparently otherwise healthy persons are due to generalized argyria? I admit that early argyria gives rise to a weird, even slightly greenish-bluish pigmentation of the face—perhaps best marked on the forehead—which apparently varies in darkness from time to time, as it did in the case of a woman I saw about thirty years ago. In such a case, as in Sir W. Langdon-Brown's case (*Brit. M. J.*, 1930, 2, 558), chronic sulphaemoglobinaemia may be thought of as a possible explanation. The woman

[1] From the *Brit. M. J.*, [illegible], 2, [illegible].

in question however, whenever she had any gastric pain, had been using a prescription given her long previously by a well known London *physician—a silver nitrate pill* *It is really quite natural* that in commencing argyria the appearance of the pigmentation should slightly vary from time to time, according to the turgidity and vascularity of the skin and the degree of illumination The skin can alter the apparent colour of pigment in or beneath it I had a dark Oxford blue spot excised from the forehead of a man, and under the microscope the blue spot was seen to be due to *brown* pigment (melanin) in nævus cells

Well marked later cases of argyria can hardly be mistaken for sulphæmoglobinæmia and are not likely to be confused with hæmo chromatosis—in *spite of the famous hæmochromatosis case* 'Blue Mary In a man I was consulted about two years ago or so the diagnosis I found had been already made out, for not only was there a history of prolonged use of a gargle or other intraoral or intranasal medicament containing silver but Dr Sheldon of Wolver hampton had been consulted regarding the possibility of hæmo chromatosis and had practically proved that the cutaneous pig *mentation was due to silver, having had a minute piece of skin* examined by the spectroscopic method Generalized argyria from silver salvarsan is known to occur though it is extremely rare

According to recent observation there seems also to be a general ized blackish pigmentation of the skin due to the prolonged use of bismuth which however rare it may be will have to be borne in mind It could be distinguished from argyria by the history and by *the spectroscopic examination of the skin (to exclude silver pigmen* tation) I am certainly inclined to believe in the genuine existence of such a rare cause of generalized cutaneous pigmentation For Professor David Riesman once showed me a man with black skin who said that he had always been accustomed to take bismuth against a chronic tendency to diarrhœa which was habitual to him There was no history of taking any silver containing drug and *the man could hardly be continuing his work as a commercial* traveller if the pigmentation was due to Addison s disease The patient was unfortunately completely lost sight of

BOUNTEOUS NATURE AND OVER-NUTRITION[1]

It is well known that the reserve power of the various organs in ordinary healthy young adults is very great Destruction or excision of one kidney does not bring on uræmia provided that the remaining kidney functions well Animal experiments and results of operations in human beings show that a great portion of the liver or the pancreas can be removed without producing signs of insufficiency of the organ in question Recovery may take place after destruction of a large area of the skin from burns in human beings Men with very small testes or with only one testis can procreate and show no signs of eunuchoidism Healthy young adults seldom call upon all the reserve power of their hearts and I would say that most persons practically never fully develop and enjoy the reserve power of which their brains—the organs of their minds—are capable We need hardly mention the obvious reserve power of our normal endocrine organs—e g the thyroid gland and the pancreatic islets

In ordinary life all the reserve power of the above mentioned organs is seldom or never called upon but with the digestive and associated metabolic functions of the body the same cannot be said Though the results of total colectomies and subtotal gastrectomies and resections of parts of the small intestine show that the reserve power of the alimentary apparatus of the body must be enormous yet in prosperous times when bountiful nature under human supervision offers abundance of food in quantity and variety these functions are not rarely strained to the uttermost Many persons from childhood onwards live the life of digestive athletes —sometimes in addition drinking the maximum amount of alcohol that they can stand (but with this latter point I am not concerned at present) The muscular system—owing to relatively sedentary occupations etc —usually fails to keep pace in helping to use up this unnecessary intake of food Over abundance of fuel causes incomplete combustion as well as total excess of waste products tending in the long run to overwork and permanently damage the metabolic and excretory organs concerned Who can doubt that such considerations do not often at least in part explain the gradual development in middle life of obesity diabetes mellitus high blood

[1] From a lett to th *Lancet* 1944 1 101

pressure and chronic gouty, arteriosclerotic and nephritic troubles, especially when there is already an inborn (possibly familial) predisposition?

No wonder then that wartime conditions—by limiting the intake of food and by increasing (in various ways) the output of energy, thus necessitating more perfect metabolism—improve the health of many persons During the last war at a hostel for foreign soldiers on leave I saw a notice somewhat like *Mangez bien mais ne gaspillez pas* A similar notice might be more appropriately posted up in peace time in many houses of all civilized countries Somewhat altered popular habits with regard to excess in eating (as well as in alcoholic drinks) have already probably contributed towards the modern increased average life expectancy for adults

I do not, however wish to overestimate the bad effects of what I call *over nutrition* which in reality is rather a kind of *wrong nutrition* Brain workers even when they take next to no muscular exercise must of course not be starved They often feel the need for stimulating food A lady told me that her husband required a great deal of meat, because he was a brain worker! Frequent and very small meals do really help to stimulate sedentary writers and brain workers certainly more so than the customary regular full meals I believe that the craving for food often felt when a continued effort has to be made in writing a long article or book (especially by those who are not authors by profession) is natural enough but should of course not be satisfied by large amounts of butchers meat A well known medical author on a subject connected with diet once told me that, when finishing a book or article, he had himself derived great help by temporarily leaving his ordinary work in London and living in a quiet place on a diet with cheese as an important constituent

It seems that overeating by some brain workers is due to a call by the tired brain for food and stimulation but doubtless the satisfying of this call by large (and meaty) meals is a great mistake and may be finally disastrous if long continued For temporary reading and writing at night stimulation by coffee or tea used to be most frequently resorted to but I think that plain milk chocolate (always easily obtainable in peacetime) is generally more useful (at least to small eaters) and less likely to disturb subsequent sleep Some day perhaps a vitamin or special substance will be discovered for brain work, which will get rid of the peculiar craving for food

that in some cases becomes tiresome It seems that the temporarily overworked brain demands a much larger quantity of food than what at the time is required by the rest of the body in the hope (if I may so express my meaning) that it may extract from this quantity a minute but sufficient amount of some precious substance which will act towards it like a vitamin and stimulant

Corollary, On Doubt in the Elderly

Among the problems connected with the subject of old age there is one that seems to me worthy, so far as possible of special investigation I refer to the calorie value of the diet during the prime of life It has been suspected that a very high calorie value—especially excess of meat—tends to shorten life death occurring at between, say 60 to 70 years of age instead of between 70 and 80 It would be very *interesting* if dietetic investigations could throw light on this subject Even during my life time habits seem to have changed considerably much less meat being consumed by well to do men in the prime of life (I refer of course to ordinary times of peace) The metabolic and excretory organs (especially the kidneys) are presumably less constantly overworked and maintain their proper functional activity to a later period of life this may partly account for the modern increase of old persons with normal mental powers

Is there any reason for endeavouring to increase the number of old persons? Yes I think so One of the chief advantages of healthy old persons in a community consists I believe in their accumulated knowledge and resultant *doubt* Doubt grows with knowledge (Goethe) and knowledge *should* increase with age Old persons owing to their knowledge and doubt should be less prone than the young to that kind of fanatical certitude which provokes enmity aggression and hasty war (After *Brit med J* 1946, 1 996 letter)

XXVIII

EUTHANASIA AND THE MEDICAL PROFESSION[1]

Some might think that a discussion on the above subject was out of place in wartime, when so many of the world's young men are being killed daily on the battlefield. Answers to a question recently put to the B.B.C. Brains Trust show otherwise. Professor Joad, who seemed to be the only one in favour of making euthanasia (under proper precautions) legal, said that we were pitchforked into life without so much as a by your leave, and it was only fair and rational that we should be enabled to get out of it, if excruciating pain from incurable disease made life hopeless and intolerable and if when still in possession of our reason we earnestly begged for a painless death. He added that when we were sending so many young men daily to their death in the war it seemed hypocritical to deny euthanasia to a few elderly persons in intolerable pain from incurable disease.

The arguments in favour of euthanasia are, of course, not really reinforced by those who in poetical pessimistic moods uphold the saying of Theognis of Megara, that it would be far better never to have been born, but, once born, the next best is to get out of life and its miseries as soon as possible. Epicurus asked why persons who hold such an opinion so seldom commit suicide. Apart from religious and stoical and mystical considerations, the most rational answer to this seems to be Sir Thomas Browne's sentence (*Urn Burial*): 'The long habit of living indisposeth us for dying.'

But I must return to the question of euthanasia in its modern limited sense. The pros and cons from the ordinary common sense points of view and from religious, mystical and moral considerations may be shortly summed up. It might be maintained by some that we are not just 'pitchforked' into life, but that the adventure of life is granted us as a privilege for the development of our souls. How can it be proved that our souls were not eager for the opportunities afforded by earthly life, that the experience of the death of the body (with or without pains) is not in some way of value to the soul for its life hereafter, and that the voluntary giving up of our present life may not in some way be punished? On the other hand, we have a fragment of Euripedes suggesting that if human beings were to know what (happiness) awaited them on the other side, no one might be left here on earth to keep the human race in existence.

[1]Letter, *Med. Press and Circ.*, 1943, 210, 418.

Whether or not we are all, *nolens volens*, pitchforked into life, we are certainly often pitched out of life by disease or accident, very much against our wishes Some of the old dance of death pictures represent Death approaching a doctor just as the latter is examining a patient s urine The long habit of living (and the habit of examining patients urines) indisposeth that doctor for dying On the whole it does not seem probable that in ordinary times of peace and plenty euthanasia is likely often to be desired by sane individuals, without urgent reasons

I regard Nature as one of the manifestations of God and believe that we human beings have been gradually permitted to acquire more and more control of Nature—of which we ourselves constitute a part One often hears Nature blamed for cruelty which we ourselves—a part of Nature—might nowadays, and possibly are intended to prevent We have been enabled to avoid much suffering and death by aseptic surgery, anæsthetics anodynes chemotherapeutic means, etc Why should we not in exceptional cases of chronic painful incurable disease relieve the patient of his life at his repeated earnest request? It has been suggested that if the duty of administering legal euthanasia devolved on doctors, people might come to regard their doctors as perhaps also their executioners and this would damage them in the useful exercise of their profession But is it right for doctors to oppose the introduction of legal euthanasia merely owing to any professional and possibly selfish fear connected with such a suggestion? Anyhow from what I have myself observed I agree with many if not most other members of our profession that the actual pains of incurable diseases and of dying have been greatly overestimated in the popular mind and I believe that euthanasia if made legal would relatively seldom be earnestly demanded

XXIX

MONEY PRODUCED BY EXPERIMENTAL PATHOLOGY[1]

IN the editorial article of March 21 (*Med Press and Circ* 1945, 213 177), the use of dogs teeth as a native form of money in part of New Guinea is alluded to in a very interesting way But these dogs teeth were only small change to the canine teeth (tusks) of boars, when the tusk had grown in a circle so as to form a kind of bracelet much prized by the natives as an ornament One of the finest circular tusks that I have seen was shown by me at the old Pathological Society of London (*Trans Path Soc Lond* 1895 46 337) *It was a boar s left lower tusk, which owing to want of opposition* from the upper tusk had overgrown so as to form a complete circle, the point having entered for 1½ inches into the permanent pulp of its root The irritation caused by the entry of the point into the root was evidenced by *transverse ridges on the root* and deposition of new dentine between the point and the walls of the pulp cavity The natives artificially produced such circular tusks by breaking off the upper tusks of young boars, so as to allow the unopposed lower tusks to grow in a circle It took several years to obtain a pair of this boar s tusk ring money as I would call it Two hundred canine *teeth from dogs were equivalent to one circular tusk With two* such tusks a pig could be bought but the finest specimens were treasured as heirlooms and were handed down in the family from generation to generation Here we have a genuine example of the *making of money from pathological experiment* (F P Weber Pathological Money, *Endocrine Tumours and other Essays* 1936 p 193)

[1] Letter *Med Press and Circ* 1945 213 223

XXX

EXPLANATION OF THE URGE TO COLLECT[1]

Amongst the beneficial primitive instincts connected with the survival of the fittest and the human evolutionary progress—after Darwin, T H Huxley etc —is the urge not only to find sufficient food to satisfy immediate needs but also to acquire a store to guard against want in the immediate future This instinctive urge to acquire and collect is of course, not limited to supplies of food but applies also to clothing and other things useful for self and family also to articles of personal adornment and jewellery Unfortunately, as the late Dr Charles A Mercier especially pointed out the means may become an end in itself, and idiots may have an urge to collect rubbish (including possibly filth) of all kinds Misers may put up with dirt, and even half starve themselves in order to collect gold, for which they have no other use than the pleasure it gives them in possessing it This is surely an extreme example of an instinctive salutary urge having become perverted so that part of a means is preferred to the end

It is to the combination of an instinctive urge to collect with æsthetic tastes and a desire for historical scientific or other special knowledge that we owe our collectors of paintings and works of art coins books objects of natural history etc and the foundation of our great libraries art galleries and museums Here one may note that proper collecting of coins and medals necessitates study of history biography geography, the rise and decadence of art languages and inscriptions and the whole subject of barter and mediums of exchange Many distinguished members of the medical profession in this and other countries have been great collectors I need scarcely instance the brothers John and William Hunter (the latter with his collection of ancient Greek coins etc now in the University of Glasgow) Sir Hans Sloane Dr Richard Mead and Sir Jonathan Hutchinson Sometimes the desire to increase knowledge—e g the knowledge of the history of medicine—acts as an added stimulus to collect I remember a speaker once at the Royal Society of Medicine (Jonathan Hutchinson junr) claiming that collectors were the salt of the earth Undoubtedly this is often true of individual collectors even if the collecting be considered mainly as a hobby and even though it must be admitted greed and jealousy as well as wholesome competition may act as stimuli Alas! the

[1] After a l[illegible] *Med Press and Circ* 1944 211 414

acquisitive instinct—gone wrong—with or without a superadded 'dog in the manger' attitude, has not rarely been the cause of murder and other crimes amongst individuals and of wars amongst nations

Listening to day to the B B C Brains Trust answers to the question—'How do you explain the urge to collect?'—has induced me to write this note The Brains Trust answers seemed to me very far from the main point which the late Dr Mercier would have preferred One member of the Brains Trust hinted that to give a complete answer he would have to broach some unspeakable psycho analytical views After that I should not be surprised to hear some one maintaining that constipation is mainly due to a miserly urge to collect, i e to subconscious unwillingness to part with the accumulated store of material in the large intestine!

SOME EPIGRAMS, ETC

EPIGRAM on the remnant of an incendiary bomb which penetrated through the roof of my hospital (midday September 13 1940), and is now used as a rest for pens [1]

One day I whistled through the air
And nearly set the place a flare
But doctors smothered me with sand
And now to rest their pens I stand
Could pens prescribe a lasting balm
Of peace they d win the highest palm
Of victory It should be *real* peace,
For war and hatred both to cease!

Epigram on the remnant of an incendiary bomb which one night in September 1940 fell on to the roof of the block of London flats where I sleep and now serves as a rest for pipes [1]

One night I whistled through the air
And tried to set the roof a flare
But porters smothered me with sand
So now to rest their pipes I stand
From bombs of war to pipes of peace!
Real peace! How else can hatred cease?

In November 1941 when I had read an essay by Professor Ryle and a poem by Samuel Butler

Farewell good cheer my colleagues dear
Tis true I trust we ll have no fear
Perhaps indeed there ll be no pain
But tell me shall we meet again?
Our names may meet like any name
On the hall s mural scroll of fame
Our souls diffused in æther vast
Will have forgotten all our past—
How one said Yea and one said Nay
And on which side we stress did lay
But all our thoughts in some wise live
Blended with those which others give

[1] After *St Barth lomew s H p t l Jou* London December 1940 p 41
After *St Barth lomew s H p tal Journ* London January 1942 p 64

Samuel Butler's poem in question was quoted in my 'Aspects of Death,' 4th edition, 1922, p 216 Professor J A Ryle's excellent essay 'Of Death and Dying' (*Lancet*, 1940, 2 401) has been humorously likened to glad tidings in telegraphic style All's well Death is mostly painless Therefore enjoy your life by living with zest without fear, but to good purpose The idea of the diffusion of the soul or mind in æther (not ether) occurs in an inscription now in the British Museum, on the Athenians who fell in battle before Potidæa, 431 429 B C My conclusion on meeting again is contained in my last two lines Æther means literally the high air of the sky, but I think it permissible to use the word symbolically for the airy Utopia (=nowhere) of a poet's dream—or for Nirvana As to arguments for immortality one can always as a last resort fall back on what one might term the scientific rationalization of metempsychotic diffused immortality—to which I referred in a review 'Science and Immortality' *Medical Magazine* London 1906, **14**, 248

In regard to the word Glomus (Masson's glomus tumour) [3]

Ulcera, *non ulci*, corrumpunt corpora nostra
Et glŏmus haud glōmus Massonem laude levavit
Ulcus nunc ulcer cur non glŏmer? Anglicus inquit

The old style consumptive

Cavernen rechts Cavernen links!
Und in der Mit ein armer Mensch

A rallying cry for two in search of truth [4]

Verum quærimus audaces et vivimus ambo

[3] *Med Press and Circ* 1943 **210** 24

[4] *Opposing Aspects of Social and Political Thought—a Correspondence* by F Parkes Weber and W Henry Lewin H K Lewis & Co 1945 p 11

After the encomium on Work and Exercise in Thomas Carlyle s
Past and Present, 1843

Let others rest if they would rust
Before they must return to dust
It s exercise that I advise,
And so will you if you are wise

Ambulare se curare
Se movere est valere
Laborare est orare
Nox et quies imminent [5]

Let me explore the mountain s height
And paths, in frosty weather,
One wide view take before the Night—
With Joy and Trust together [6]

F Parkes Weber *A p cts of D th* London third edition 1918 p 357
Some Thoughts of a Doctor London 1935 (from title page)

XXXII

PALINDROMIC RHEUMATISM[1]

PALINDROMIC rheumatism is a convenient term for some clinical syndromes of uncertain causation and for component parts of more complicated 'compound syndromes

Hench and Rosenberg (1944) described thirty four cases of a new recurrent disease of joints and adjacent tissues multiple afebrile attacks of acute arthritis and periarthritis In some cases there were also recurring para arthritic swellings of soft tissues in the neighbourhood including in a few patients small temporary intracutaneous or subcutaneous nodules The attacks developed suddenly, generally lasting only a few hours or days but recurring repeatedly at short or long *irregularly* spaced intervals They were manifested by pain swelling, redness, and disability of one (some times more than one) small or large joint Little or no constitutional reaction or abnormality was revealed by laboratory tests and no *significant functional pathological or radiographic evidence of* disease was found even after scores of attacks in spite of the transitory presence (in some cases at least) of an acute or subacute inflamma tory polymorph exudate in the articular tissues and cavity

The incidence was about equal in the two sexes The patients on admission were aged 21–73 (average 42) The age at onset of the disease was 13–68 (average 34 9) The recurrence notably changed its frequency in four patients The intervals between attacks differed materially in different cases and from time to time in the same case As already mentioned usually only one joint was involved in an attack Almost any joint in the body was liable to be affected Finger joints (notably proximal interphalangeal joints) were especially frequently involved and then in order of frequency came wrists shoulders knees, toes and elbows Tendon sheaths were also occasionally affected by sudden similar attacks

Terminology

Hench and Rosenberg (1944) who introduced the name palindromic rheumatism point out that palindromic is simply Greek for recurrent and they prefer the relatively vague and non committal word rheumatism (as in frequent medical and

[1] From the *Lancet* 1946 2 931

Many terms in medical as ell as popular use are somewhat vague and str ctly speaking inexact Thus the term aortic coarctation is often used by medical writers to mean stenosis of the aortic isthmus though it strictly sign fies nothing more than aort c otenosis (stenosis of the aortic valves and or fice)

popular use) to the more exact word arthritis' Indeed the symptoms are not absolutely limited to the joints for there are sometimes pararthritic (para arthritic or para articular) swellings and nodules and the tendon sheaths—and sometimes bursæ notably the olecranon bursa (see below)—may be involved

It seems to me that the term palindromic rheumatism might well be used in a wider sense to include attacks of intermittent or recurrent hydrarthrosis (whether strictly periodic or not) as described by Schlesinger (1899) Garrod (1910) and many others the term might also be used for some at least of the cases described by Solis Cohen (1914) in his paper on angioneural arthroses commonly mistaken for gout or rheumatism and for Kahlmeter s (1939) attacks of allergic (?) rheumatism One may note by the way, that the curious recurrent attacks described under the heading Urticaria tuberosa of Willan (Nixon 1916) have analogies with angioneurotic œdema and para articular phenomena of intermittent hydrarthrosis and palindromic rheumatism

It is true that some of Solis Cohen s cases were febrile whereas the attacks in Hench and Rosenberg s patients were afebrile as were most of the intermittent hydrarthrosis attacks referred to by Garrod and others Most of the cases of intermittent hydrarthrosis were definitely periodic whereas the intervals between the attacks in Hench and Rosenberg s cases were irregular Though the differences between these various classes may be considerable enough perhaps to separate them roughly into various clinical syndromes the points of resemblance are I think sufficiently marked to justify their collection into various syndrome groups under one heading palindromic rheumatism

Ætiology

Can there be any common ætiological factor in all these cases? There is some resemblance between individual attacks of palindromic rheumatism and the acknowledged allergic joint symptoms of serum disease Many have noted an analogy with angioneurotic œdema which a few of the patients also had Schlesinger (1899) was struck by resemblances between angioneurotic œdema and intermittent hydrarthrosis and suggested that some cases of intermittent hydrarthrosis were really angioneurotic œdema of synovial membrane In the families of some patients with palindromic rheumatism (in my enlarged sense) there have been allergic manifestations such as urticaria angioneurotic œdema asthma and

I think, recurrent vomiting. Apart from allergy in family history, it may be noted that some of Kahlmeter's (1939) patients had urticaria, angioneurotic œdema, asthma, or migraine. It must be admitted that palindromic rheumatism (in my wider and more inclusive sense) is intimately allied to allergy or some process resembling allergy, even if no causal allergens for the attacks have yet been discovered. Focal sepsis has probably been a causal factor in some cases, owing to bacterial allergens being discharged at times into the blood stream. One may suspect an inborn tendency *as a factor in a few cases in which a family history of similar attacks* and acknowledged allergic conditions was forthcoming. Frenkel Tissot (1916) reported that in a group of four sibs, three had had intermittent hydrarthrosis (knee), and the other was subject to periodic attacks of migraine and occasional urticaria.

Symptoms

Garrod (1910) agreed with previous writers in dividing cases of intermittent hydrarthrosis into primary and symptomatic cases.

In primary cases the periodic swelling comes on as an isolated event, sometimes after an injury, and the affected joints, which are in the great majority of instances the knees, recover completely or almost completely in the intervals, at any rate in the earlier stages. In symptomatic cases, on the other hand, the affected joints have already been damaged more or less severely by antecedent disease, such as the more obstinate forms of gonorrhœal arthritis, or the crippling lesions of many joints commonly classed as rheumatoid arthritis or arthritis deformans. In other respects the cases of the two classes closely resemble each other, and the *observation of a series of examples inclines one to the opinion* that, as Linberger (1901) maintains, intermittent hydrarthrosis is a phase or symptom of various diseases rather than a disease *sui generis*.

A woman, aged 67, in hospital at present with old osteo arthritis and pernicious anæmia, was under my care about 1919 (when she was aged 40) with recurrent, but not periodic, attacks of swelling, stiffness, and pain in the left knee, each attack lasting a few days. The radiologist *(Dr. James Metcalfe) suggested intermittent synovitis.*

Garrod (1910) draws attention to abrupt changes in the features sometimes seen, possibly in connexion with therapeutic measures, when the intermittent hydrarthrosis ceases and is resumed after a

more or less long pause The frequency may change or the attacks may recur on the opposite side of the body I was once shown an excellent example of such a change (a case of Dr O B Bode) Of concurrent conditions, Garrod writes, pregnancy exercises the most conspicuous influence on the course of intermittent hydrarthrosis In most recorded instances, the articular attacks have ceased during pregnancy, but not always throughout the whole period of preg nancy In certain cases hydrarthrosis attacks have shown relation to menstrual periods Attacks have been more severe or less severe when they coincided with menstrual periods

The small temporary pararthritic intracutaneous and subcutaneous nodules, investigated by Hench and Rosenberg in some of their cases remind me of the little nodules which sometimes suddenly develop and spontaneously disappear in cases of rheumatoid arthritis and which may represent an early stage of the well known chronic necrobiotic subcutaneous nodules of the rheumatoid arthritis type (Weber 1946), though they become reabsorbed without the development of necrotic foci

Some More Complicated 'Compound' Syndromes

Palindromic rheumatism in my proposed extended sense is also a convenient term for prominent features of certain more complicated syndromes which are probably almost unique I will give two examples

The first case can be described as one of palindromic rheumatism without permanent changes in or round affected joints with recurrent allergic ?) attacks of Meniere s syndrome without resulting deafness and with recurrent (allergic ?) attacks of iritis with pain but without permanent synechiæ or permanent changes in the eyes

CASE 1

A man aged 28 with the above mentioned complaints was admitted to hospital on August 6 1946 for investigation He had been born in Burma of British parents and had been married one year—no children

History—Seventeen years ago he had begun to have attacks of pain in the hip joints especially the right one The pain had been felt in the joints rather than about the joints or in the bones) sometimes radiating down the thigh from the affected hip joint The pain had been boring and especially sharp on moving Besides the pain there had been a sensation of stiffness No local tenderness

no definite periodicity, but on the average about six months' interval between attacks which had lasted usually a few weeks Nothing abnormal had been detected on radiography The attacks had apparently been afebrile and not accompanied by constitutional symptoms No definite diagnosis seems to have been made Rest in bed for five months had been at first ordered, but had been followed by no obvious improvement Rest had therefore not been regularly adopted for treatment The pain had usually been in the right hip joint but sometimes in the left Both sides had never been affected together No other joints had ever been involved Last attack had been about three weeks ago right more than left hip Both hip joints had been affected but one side had been completely free (after two week) before the other had become painful (for a week) Patient does not go to bed for the attacks though occasionally owing to the pain he has had to rest

The attacks of Meniere s syndrome had never come on at the same time as the joint pains The first sharp attack had been twelve years ago accompanied by vomiting Patient had woken up one morning unable to sit up or turn over in bed he had vomited four or five times but the vomiting had not been accompanied by a sensation of nausea that attack had lasted thirty six hours The next attack had been a few months later The interval between attacks had varied from a few months to two years up to three or four years ago but since then the attacks had been more frequent though less severe excepting for one severe (the last) attack six weeks ago The average duration of the attacks had been 24–30 hours but they might last up to three days No causal factors had been discovered Prodromal symptoms had been a kind of light headedness and tinnitus slight at first but becoming more pronounced as the attack gradually developed There had been no associated deafness either during or after the attacks—hearing not impaired No associated headache, no associated incontinence Of the vertigo, patient said that his surroundings seemed at first to revolve but, when he lay down objects seemed to pass back over his vertex from the front The attacks appeared to be relieved by lying flat on the back—? aborted by pilocarpine gr $\frac{1}{10}$

Seven years ago he had developed the first of seven or eight attacks of iritis That attack had been on the right side and had lasted about eight weeks Patient had had only one attack on the left side, the two sides had never been affected simultaneously

The attacks had been accompanied by considerable eye pain, especially on coming into the light from a dark room They had occurred at about yearly intervals average duration about a month They had varied in intensity No precipitating factor known The last attack had been in January 1946

The eye, ear, and joint attacks had never accompanied one another not more than one of the three kinds had occurred at a time

Patient s general health apart from the above troubles had been good and there had been no other serious complaint There was nothing in the family history specially bearing on the subject We heard privately that the family was delicate A sister had recently had pericarditis after sinusitis at the age of 23 Patient s mother had died young cause uncertain Patient had seen various specialists A salt free diet had not helped Dr Norman William Gardener had always treated patient for his eyes—with atropine ointment and by steaming Dr Gardener is certain that the eye attacks were definitely iritis possibly tuberculous There had been definite iritic exudate (plastic iritis) but no permanent synechiæ This iritis had affected only one eye at a time He cannot remember whether there had been any sluggishness in pupillary reaction change in colour of the affected iris or any inequality of pupils before atropine treatment had been begun

On Admission to Hospital.—Height 5 ft 6½ in weight 8 st 12 lb Tall hyposthenic type rather delicate looking No evidence of anæmia Teeth tongue tonsils and throat nothing special No obvious enlargement of any superficial lymph glands No evidence of latent tetany Cardiovascular system nil special Brachial blood pressure 135/80 mm Hg Respiratory system nil special Abdomen nil special No achlorhydria (August 10 1946) Central nervous system nil special Eyes very slight lateral nystagmus slight myopia Hearing good on both sides Nervous reflexes (deep and superficial) normal Urine acid trace albumin a few hyaline casts But on another occasion nothing abnormal was found sp gr 1020 acid No other abnormal urinary symptoms Radiograms of both hip joints and of skull (Dr F G Wood August 6 1946) nothing abnormal Blood Wassermann reaction negative (July 17 1946) Blood sugar 110 mg per 100 c c Blood uric acid (August 16 1946) 3 2 mg per 100 c c Sedimentation rate (August 7 1946) first hour 6 mm two hours 17 mm (hourly average 7 mm) Blood-count

(August 17, 1946) red cells 4 950,000 per c mm , Hb 96 per cent colour index 0 97, leucocytes 7 000 per c mm On August 21, 1946 the leucocytes were 7 900 per c mm (polymorphs 76 per cent lymphocytes 23 per cent, eosinophils 1 per cent)

Patient is now under observation at home, apparently at present in good health

The symptoms in this case are clearly enough defined to constitute a definite triad syndrome but no other exactly similar case seems to be known It is difficult to avoid the conclusion that each of the three syndromes constituting this compound triad syndrome is allergic though no focal sepsis or allergen has been discovered

Quincke (1921), among the numerous unusual localizations of his angioneurotic œdema does not seem to have mentioned the internal ear and Meniere s syndrome Duke (1923) suggested an allergic origin for some cases of Meniere s syndrome He referred to a man and a woman with definite allergic history in whom Meniere s attacks seem to be caused by certain articles of food The attacks were relieved by adrenaline and by the avoidance of the foods in question attacks could be reproduced by eating such foods or by intracutaneous injection of extracts Williams (1945, 1946) has recently elaborated an allergic explanation linking Meniere s disease or rather syndrome—which he terms endolymphatic hydrops of the ear—with vasomotor rhinitis etc as manifestations of physical allergy in the head

In regard to the recurrent attacks of iritis I think they are most probably also allergic Though I know of allergic cataract (so called dermatological cataract) occurring in subjects with allergic derma toses (eczema prurigo syndrome with or without asthma nevroder mite), and of allergic conjunctivitis—e g that associated with hay fever—there is apparently no ophthalmological literature recording recurrent iritis as in this patient (compare Ridley and Sorsby, 1940) If the patient s joint attacks had been real (? streptococcal) rheumatism instead of palindromic rheumatism, the attacks of iritis might have been supposed to be rheumatic iritis and therefore allergic in so far as acute rheumatism is now generally supposed to represent an allergic response towards the pathogenic agent of acute rheumatism (? some hæmolytic streptococcus or virus) It may be noted, however that Parry (1939) recorded recurrent attacks of iridocyclitis in a young woman apparently allergic and due to hypersensitivity to egg white

In short this case strongly supports Schlesinger's original views of 1899 according to which the condition would be angioneurotic œdema or, as he preferred to call it, hydrops hypostrophos—i e, recurrent œdema—sometimes of the synovial membrane of a hip-joint sometimes of one iris and at other times of one internal ear the cochlea beginning to be affected before the semicircular canals The iris attacks it must be admitted are rather chronic but probably in some localizations angioneurotic œdema may be relatively chronic An allergic reaction may doubtless be chronic if there is persistent action of some known or unknown allergen in an allergic subject Recurrent acute reactions can give rise to chronic (persistent) changes I believe that Loeffler's transitory pulmonary infiltrations with eosinophilia are nothing else than angioneurotic œdema but apparently attacks are not always quite so transitory—compare the case of a man aged 19 with a history of hay fever, shown by A Ikeles and N R Butler at the Clinical Section of the Royal Society of Medicine on April 12 1946 as an example of recurrent transitory pulmonary infiltrations with eosinophilia (chronic type of Loeffler's syndrome)

The second case is one which the late Lord Dawson discussed with me in 1942 as a puzzling rarity

CASE 2

The patient was a tall strong looking man aged about 60 who since 1936 had had attacks of swellings of the hands or feet usually only one side at a time The forearms knees and legs had been similarly affected Sometimes also there had been sudden enlargement of an olecranon bursa (no evidence of gout discovered) There had also been subcutaneous nodules along the ridge of the ulna from the elbow these had been situated over the periosteum and not in it though somewhat adherent to it Sensation of tightness in an arm leg or shoulder had sometimes given warning of an impending attack The attacks had never been accompanied by fever or definite pain (contrast this with true attacks of gout) The attacks had lasted a few days and slowly passed off

I saw him during one attack which was of three or four days duration and was beginning to subside Some fingers of both hands were involved in one hand more than in the other The skin over the swelling was red and shiny in some parts but some patches or streaks were pale as if blood had been driven out of the surface capillaries by the pressure of serous effusion Patient had also a

chronic smooth bony enlargement (not painful or tender) of the upper end of one fibula, which is difficult to explain

Previous Data —A symptomless stone in the gall bladder had been discovered on routine radiography Liver efficiency was normal Gastric achlorhydria was reported but some free acid returned after gastric lavage Blood uric acid 3 6 mg per 100 c c Blood sugar normal Radiography showed no articular changes and nothing abnormal in the bones but the swelling in the fibular had apparently not been examined Brachial systolic blood pressure about 130 mm Hg

On one occasion an enlarged olecranon bursa had been tapped and had yielded a serous fluid giving a pure culture of *Staph aureus* No definite evidence of allergy had been discovered by skin tests One antrum was opaque and had been cleared and curetted for a polypoid condition but that had had no effect on patient s attack A pure growth of *Staph aureus* had been obtained from the antrum 'Atophan had seemed to diminish the attacks at first, but not later

The attacks had never laid the patient up but if his fingers had been much swollen during an attack he could hardly use them, and could not write He took an ordinary diet as he had found that diet made no difference He had also left off taking dilute hydro chloric acid with meals as he thought that also had made no difference While he had been in South Africa he had remained free from attacks but after he had left they had begun again Exposure to cold had sometimes definitely brought on an attack

This case seems to come half way between palindromic rheuma tism and angioneurotic œdema According to Schlesinger s views of 1899 the patient would be suffering from recurrent angioneurotic œdema (or hydrops hypostrophos as he called it) of the peri and para arthritic tissues of his fingers and limbs and notably sometimes of the synovial lining and wall of one of his olecranon bursæ The appearance of subcutaneous nodules over the ulnar ridge from the elbow downwards as in some cases of rheumatoid arthritis, is a feature of the case (cf Weber 1946) The swelling of the upper end of one fibula is unexplained

Summary

In spite of obvious objections which might be raised by the fastidious in nomenclature it is convenient to retain the rather loose term palindromic rheumatism proposed by Hench and

Rosenberg (1944) Perhaps, however it would be better to enlarge the scope of the term, to include nearly related syndromes such as intermittent hydrarthrosis (hydrops articulorum intermittens), which Schlesinger (1899) suggested was a recurrent angioneurotic œdema (hydrops hypostrophos he termed it) of the synovial membrane and soft parts of joints

Palindromic rheumatism in the extended sense that I propose constitutes also a convenient term for the central features of certain more complicated (compound) syndromes two remarkable *examples of which are described*

I am indebted to Dr E Schwarz for permission to publish the record of Case 1

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Postscript—An elderly medical friend told me of his recent experience He had a slight cold accompanied by cough and slight sore throat About a week later he was suddenly attacked by sharp pain and swelling in the left patellar bursa accompanied by local heat and redness with slight fever He did not stop in bed and in a week s time he felt quite well again Then however he developed tenosynovitis about the left ankle which gradually passed off He had since early life been subject to migraine like attacks though not unilateral With this exception he had enjoyed good health As a young man he had had tenosynovitis in the wrist from fencing and on the inner side of the knee when learning to ride In this instance I suggest that the bursal swelling in front of the knee and the tenosynovitis were local allergic like phenomena of the nature of angioneurotic œdema He may have become hyper sensitive towards some agent introduced by the cold

Slight traumata may be supposed to act locally by causing the formation of some histamine like substance, which *in hypersensitive subjects* produces local œdematous inflammatory reaction and, if the process be frequently repeated, chronic fibrous thickening as manifested in the permanently thickened bursa of housemaid's knee, thickening of the olecranon bursa and the chronic changes of Dupuytren's contraction and Landouzy's acquired form of camptodactylia [1]

[1] In this connection I would suggest that certain transient attacks of sharply localised itchy pain are due to a condition in *the palmar fascia and tendon sheaths of the fingers* analogous to urticaria

XXXIII

THE QUESTION OF ACUTE AND CHRONIC ALLERGIC OR ALLERGIC-LIKE CONDITIONS AND THE BEARING OF THE QUESTION ON CLASSIFICATION AND THERAPY[1]

Allergic Pulmonary Infiltrations—In a recent letter to the *British Medical Journal* (1946 2, 555) concerning infestation with round worms and its relation to pulmonary infiltrations and urticaria like phenomena I wrote Of individuals with ascariasis it is surely only those who are hypersensitive (allergic) towards the ascariasis who develop pulmonary infiltrations of the Loeffler type and other allergic manifestations *and most persons are not hypersensitive* See the discussion on the subject by Spuhler and Kartagener in the *Schweiz Med Wochenschrift* 1944 74, 1145

The prevailing idea is I believe that such pulmonary infiltrations (pneumonitis if one prefers to use the term) are nothing but angioneurotic œdema in the lungs in subjects who are hypersensitive towards ascariasis or other allergens including those of hay fever and asthma Such pulmonary infiltrations need not always be merely transitory —compare the case of a man aged 19 years, with a history of hay fever shown by A Elkeles and N R Butler at the Clinical Section of the Royal Society of Medicine on April 12 1946 under the heading Recurrent Transitory Pulmonary Infiltrations with Eosinophilia—Chronic Type of Loeffler s Syndrome

Epituberculosis—The pulmonary infiltrations to which the name epituberculosis has been attached have been the subject of much controversy (*see* A R Rich 'The Pathogenesis of Tuberculosis 1944 pp 831 830) The name was suggested by Eliasberg and Neuland in 1920 (*Jahrb f Kinderheilk* 93 88) to signify their belief that it was not a true tuberculous condition Authorities on the subject are now against the view that the condition may represent a chronic allergic response towards a tuberculous focus

Acute Paroxysmal Pulmonary Œdema—Some cases of acute paroxysmal pulmonary œdema seem to be examples of acute allergic reaction at the commencement of an attack of pneumonia or bronchopneumonia (cf a review of the subject by F P Weber, *Clinical Journal* 1922 51 397) H Muller (*Korresp Bl schweiz Ar*. 1891 21 432) described an attack of an acute pulmonary

[1] Enlarged after the *Medic l P ss* 1946 216 361

œdema associated with angioneurotic œdema of the face It is possible that other attacks of acute paroxysmal pulmonary œdema may also be of allergic nature, though influenced by high pressure in the pulmonary circulation in subjects of mitral stenosis or chronic renal disease

Acute Articular Rheumatism —There is much in favour of the view that the articular and cardio valvular (and iritic) phenomena of acute rheumatism are allergic reactions towards the infective agent (? streptococcus or virus) of acute rheumatism in specially allergic subjects If this is so, what is the manifestation of the infection of acute rheumatism in ordinary—non allergic—subjects? Can it be merely a tonsillitis or pharyngitis? To account for the modern decrease in the severest type of acute articular rheumatism in children, one may ask Are the ordinary London children of to day less allergic towards such throat infections owing to better general nutrition and less avitaminosis? Secondly Is prophylactic treatment better carried out by tonsillectomy and by sulphonamides and penicillin?

Are Aschoff's bodies merely a more permanent expression of allergic inflammation in the heart—or in the lungs in cases of associated (rheumatic) pneumonia?

Allergic Necrobiotic Reactions —Are the cutaneous and subcutaneous necrobiotic nodules in rheumatoid arthritis (*see* F P Weber *Lancet*, 1944 2 611) the expression (or result) of an allergic response towards the unknown pathogenic agent of rheumatoid arthritis—as the more temporary nodules of acute rheumatism are almost certainly an allergic response towards the pathogenic agent of acute rheumatism?

There seems to be an allergic element in the necrobiotic changes found in the nodes of certain cases of peri arteritis nodosa

Palindromic Rheumatism —Elsewhere I have endeavoured to sum up the evidence in favour of palindromic rheumatism (Hench and Rosenberg 1944) and recurrent or periodic hydrarthrosis of Schlesinger (1899) and A E Garrod (1910) and certain pararthritic swellings, all being of allergic or allergic like nature—in fact a kind of angioneurotic œdema of the synovial membranes of joints, tendon sheaths and bursæ and of peri articular and para articular structures

Gout —There is doubtless as has been long suggested, an allergic element in acute and *subacute gouty attacks of all kinds*

Migraine—It is possible that there is an allergic type of migraine connected with œdematous swelling on the painful side of the brain Dr D S Russell has told me of a case in which, during attacks a calcified pineal body was seen by X ray examination to have slightly shifted its position away from the migrainous side

Varicella and Herpes Zoster—The generalized varicella like eruption sometimes associated with herpes zoster in middle aged or elderly persons is itchy and strikingly like strophulus (papular urticaria) in children There is considerable evidence in favour of its being true varicella but it might possibly represent a generalized allergic response towards the virus of herpes zoster in hypersensitized individuals

Therapeutic Implications—Is the action of sodium salicylate and aspirin and atophan (cinchophen) mainly an anti allergic one? In this connection one may remember the ordinary nerve soothing effect of aspirin on certain occasions which Sir Lauder Brunton, I believe suggested was due to a loosening of the synapses in the brain (cf F P Weber *Med Press & Circ*, 1933 **187** 306 and 1934 **188** 60) When penicillin and sulphonamides do good in allergic cases is the favourable effect due to suppression of some latent infective focus causing an allergic response in allergic individuals? What is the anti allergic value of calcium therapy in various cases? Adrenalin does not seem worth using in most of the above ca es in spite of its value in asthma etc

Chronic Allergic Reactions—I believe there are chronic as well as acute allergic reactions The recurrence of acute reactions can give rise to chronic (persistent) changes In fact there are chronic pulmonary infiltrations chronic subcutaneous œdemas and chronic local inflammatory or necrobiotic processes which can be best explained as chronic allergic reactions towards the frequently recurrent or *persistent* action of some known or unknown agent (allergen) in a subject who is allergic towards that agent

Classification—In the foregoing I have endeavoured to modify the theoretical classification of certain pathological phenomena believing that although premature synthesis is undesirable temporary grouping is better than chaos

XXXIV

SCLERODERMIA AND THE SYMPTOMATIC SCLERODERMAS[1]

UNDER the above heading the various forms of symptomatic *scleroderma* (a better term than 'pseudo scleroderma') are included If one uses this terminology one is doing something analogous to what Kinnier Wilson (*Neurology* 1940 p 1469) and others have done in speaking of the epilepsies to include all symptomatic epileptiform conditions and in using the term 'Parkinsonism, or the Parkinsonian syndrome to include paralysis agitans (Parkinson s disease) and symptomatic Parkinsonism arising from lethargic encephalitis and other causes (cf H Dimsdale, *Quart Journ Med*, 1946 **15** 155)

Symptomatic Sclerodermas

Symptomatic sclerodermic conditions may be of chronic hypostatic origin and connected with varicose eczema and varicose dystrophy If myocardial insufficiency complicates such a symptomatic scleroderma of a leg the hide bound condition prevents local œdema and this (hide bound) portion contrasts with the œdematous swelling in the upper (proximal) part of the limb especially the thigh This puzzled me in one case at first but cardiac treatment removed the œdema whilst it left the sclerotic portion of the skin unaltered

Any very chronic œdema may lead to a sclerotic symptomatic scleroderma especially if complicated by recurrent erysipelas like attacks For instance the later stages of the congenital or early developmental and often heredo familial œdemas of the Nonne Milroy Meige type sometimes constitute a good example of this

Chronic obstructive œdemas sometimes leading to sclerodermic and elephantiastic conditions include those due to filariasis lymphogranulomatosis inguinalis (lymphogranuloma venereum) syphilis and chronic or recurrent lymphangitis of various non tropical kinds

Some local sclerodermic patches are doubtless of tuberculous origin for instance the scleroderma like form of erythema induratum of the legs Pre tibial and other plaques (occasionally

[1]After the *Medical Press* 1946 **216** 341 *Part of the Annual Oration at the Reading* Pathological Society October 24 1946

lichen like) and thickened areas are now well known in dysthyroidal especially hyperthyroidal subjects sometimes after thyroidectomy

Scleroderma like changes in the legs have sometimes been found as a manifestation of primary idiopathic amyloidosis (for literature, *see* Weber, Stott Cade and Pulvertaft *Quart Journ Med* 1937, 6, 181)

In obese subjects especially women including certain hypothyroid cases and subjects of supposed Dercum s disease sclerotic changes not rarely develop in parts of the subcutaneous fat—notably in diffuse lipomata if present These areas of chronic panniculitis are I suspect often partly of ischæmic origin The local blood supply fails to keep pace with the rapid growth of fat, and small nutrient blood vessels may thus become occluded by pressure of the fat cells, chance trauma doubtless often acting as determining cause In such areas of sclerosed fat there are probably sometimes cholesterol-containing cells

These cases bring one on to other kinds of *necrotic fat sclerosis*, especially the kind of sclerema neonatorum which is rightly termed adiponecrosis subcutanea neonatorum (*see* A M H Gray, *Arch Derm and Syph*, 1926 14 635 and *Brit Journ Derm and Syph* 1933 45 498 G A Harrison and J W McNee *Arch Dis Child* 1926 1 63 H Fox, *Arch Derm and Syph* 1933 27 237) and subcutaneous fat necrosis of traumatic origin in adults notably of the breast in women (the sclerotic condition resulting from which has sometimes been mistaken for cancer) Paraffin and foreign fats and oils injected into the subcutaneous tissue may as is well known lead to reactionary sclerotic conditions

In congenital allergic cases with the eczema prurigo asthma syndrome recurrent and chronic urticaria and eczema may lead to the development of pruriginous hard nodular scleroses and ichthyosiform scleroderma like patches on extremities and trunk There are certainly intermediate stages between urticarial chronic urticarial and pruriginous rough scleroderma like dermatoses

The above is a very concise and somewhat incomplete grouping of symptomatic sclerodermas but I have said nothing as yet of the disease sclerodermia We do not really know its ætiology and naturally whether all its so-called varieties are to be regarded as examples of a single disease

Sclerodermia

The most typical cases are those of generalized symmetrical sclerodermia of sclerodactylia distribution in adults, but similar cases may start in childhood, in one case the disease seemed to have already commenced at or before birth Some generalized cases in which the muscles were perhaps involved have been labelled chronic symmetrical dermatomyositis—but such cases are very different from typical dermatomyositis In the case of *dermatomyositis* recorded by F P Weber and A M H Gray in 1924 (*Brit Journ Derm and Syph*, **36** 544 with an account of the literature up to date), the patient a woman aged 22 years became a case of generalized symptomatic scleroderma but finally recovered completely except for some remaining stiffness I agree with Dowling and others that some cases of symmetrical chronic sclerodermia like changes especially of sclerodactylia like distribution in the upper extremities are really forms of or results of dermato myositis or poikilodermatomyositis (cf Dowling and Freudenthal, *Brit Journ Derm* 1938 **50** 519 Dowling and Griffiths *Lancet*, 1939 **1**, 1424, Dowling *Brit Journ Derm* 1936 **48** 648 and 1940 **52**, 242 Lewis *ibid* 1940 **52** 233 Freudenthal *ibid*, 1940 **52**, 289)

Intimately allied to sclerodermia are certain atrophodermic cases Acrodermatitis atrophicans chronica (Herxheimer) and the still more atrophic erythromelie (Pick) In sclerodermia and allied conditions such as acrodermatitis atrophicans chronica sub cutaneous fibrous nodules superficially recalling rheumatic nodules have occasionally been noted in children as well as in adults

Circumscribed or morphœic sclerodermia has many varieties including perhaps the so called lichen sclerosus The mucosæ may be involved H W Barber (*Proc Roy Soc Med* 1943 **37** 73) showed a man aged 43 with a morphœic patch in the oral mucous membrane on one side of the frenum linguæ

Sometimes atrophic stripes and patches of subcutaneous tissue may so to speak take the place of morphœic cutaneous patches constituting morphœic atrophy of subcutaneous tissue I have seen examples of this and am inclined to regard the condition as self limiting as is ordinary linear morphœa Both these morphœas and the ivory like linear morphœa of the forehead involving both

cutis and subcutaneous tissue, tend to commence in childhood or youth and ultimately to come spontaneously to a standstill

In regard to morphœic atrophy of subcutaneous tissue (panniculus *adiposus), and sometimes muscle with or without actual cutaneous* involvement it may be noted that Stanley Barnes (*Brit Journ Derm* 1939 51 377) recorded his re examination of a woman in 1931 when she was aged 78 whom he had examined twenty nine years previously for Sir W R Gowers (S Barnes *Trans Clin Soc Lond* 1903 36 164) During those twenty nine years there had been no extension of the morphœic fat atrophy and the patient had remained remarkably healthy This well illustrates the self limiting nature of the morphœic disease

The occasional association of morphœic sclerodermia with facial hemiatrophy is of extreme interest as this connexion may ultimately throw further light on the nature of both conditions In a boy with facial hemiatrophy whom I saw recently there was a sagittal bony groove close to the middle line of the cranial vault on the side of the facial hemiatrophy reminding one of the well known unilateral morphœic stripes on the forehead and scalp

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